PART II – NEUROLOGICAL DISORDERS

CHAPTER 18
INHERITED NEUROLOGICAL DISORDERS

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NEUROLOGY IN AFRICA
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CONTENTS

INHERITED NEUROLOGICAL DISORDERS ........................................ 399
NEUROFIBROMATOSIS TYPE 1 ............................................. 399
NEUROFIBROMATOSIS TYPE 2 ........................................... 402
TUBEROUS SCLEROSIS .................................................... 403
STURGE WEBER SYNDROME ........................................... 403
SPINOCEREBELLAR DISORDERS .......................................... 404
FRIEDREICH’S ATAXIA ..................................................... 404
INHERITED NEUROPATHIES ............................................. 405
HUNTINGTON’S DISEASE (HD) ........................................... 405
OTHER HEREDITARY NEUROLOGICAL DISORDERS .............. 406
HEREDITARY SPASTIC PARAPARESIS (HSP) ......................... 406
WILSON’S DISEASE ......................................................... 407
CHAPTER 18

INHERITED NEUROLOGICAL DISORDERS

Inherited neurological disorders are generally relatively uncommon (Table 18.1). Their frequency in Africa is largely unknown. Inheritance follows the basic Mendelian laws for autosomal dominant, autosomal recessive and X-linked recessive inheritance. An example of an autosomal dominant disorder is neurofibromatosis and of an autosomal recessive disorder is Friedreich’s ataxia. Duchenne’s and Becker’s muscular dystrophy (Chapter 13) are both X-linked disorders. Huntington’s disease is an example of an autosomal dominant and a trinucleotide repeat disorder. A positive family history can usually be elicited in the autosomal dominant and X-linked disorders, underlining the importance of the family history. The aim of this chapter is to review the more commonly encountered hereditary neurological disorders. The student should aim to recognize and be familiar with the main ones.

| Table 18.1 Characteristics of the main inherited neurological disorders |
|-----------------------------|-----------------|----------------|-----------------|-----------------------------|
| Disorder                    | Genetics        | Age of onset   | Frequency*     | Main clinical features      |
| Neurofibromatosis type 1    | autosomal       | children & adults | 1/4000         | neurofibroma on nerves, café-au-laït spots >5, axillary freckling |
| Neurofibromatosis type 2    | autosomal       | adults          | 1/50,000       | deafness, bilateral acoustic neuromas |
| Tuberous Sclerosis          | autosomal       | children & young adults | 1/15,000   | epilepsy, adenoma sebaceum on face, hamartoma |
| Friedreich’s ataxia         | autosomal       | teens            | 1/50,000       | cerebellar signs, progressive gait ataxia, upper motor neurone signs, absent ankle jerks |
| Charcot-Marie-Tooth disease | autosomal       | young adults     | 1/3,000        | peripheral neuropathy, marked lower limb distal wasting, high arched feet (pes cavus) |
| Huntington’s disease        | autosomal       | middle aged adults | 1/10,000      | choreaform movements, progressive dementia, psychiatric symptoms |

* frequencies based on studies in high income countries

NEUROFIBROMATOSIS TYPE 1

Neurofibromatosis type 1 is an autosomal dominant disorder with an age-dependent penetrance caused by a defect in the NF1 gene (neurofibromin) on chromosome 17q occurring with a frequency of about 1 in 4-5,000 (Table 18.1). Its frequency in Africa is likely to be similar. About 30-50% of cases are the result of new mutations. Clinically, it is characterised
by neurofibromata lying on peripheral nerves, multiple cutaneous fibromas, and more than 5 hyperpigmented or café-au-lait (CAL) spots on the trunk (Fig. 18.1); see NIH clinical criteria and main clinical features NF1 (Table 18.2). The clinical picture can vary from very few to very many and distinctive skin lesions. Other clinical findings include axillary, neck and groin freckling, Lisch nodules on the iris and sometimes a scoliosis. Patients with type 1 may develop paraplegia secondary to an expanding intra axial neurofibroma arising from a nerve root pressing on the spinal cord (Fig. 18.1). They are also at risk for large deforming plexiform neuromas (Fig. 18.1), sarcomas, brain gliomas and pheochromocytoma.

Table 18.2 Diagnostic criteria for NF1

<table>
<thead>
<tr>
<th>Criteria: a diagnosis of NF type 1 is met if any two or more of the following is met.</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 or more CAL* spots</td>
</tr>
<tr>
<td>1.5 cm or larger in post pubertal patients</td>
</tr>
<tr>
<td>0.5 cm or larger in prepubertal patients</td>
</tr>
<tr>
<td>2 or more neurofibromata of any type</td>
</tr>
<tr>
<td>or</td>
</tr>
<tr>
<td>1 or more plexiform neurofibroma</td>
</tr>
<tr>
<td>freckling in axilla, neck or groin</td>
</tr>
<tr>
<td>optic glioma</td>
</tr>
<tr>
<td>2 or more Lisch nodules</td>
</tr>
<tr>
<td>a distinctive bone lesion</td>
</tr>
<tr>
<td>dysplasia of the sphenoid bone</td>
</tr>
<tr>
<td>dysplasia or thinning of long bone cortex (tibia)</td>
</tr>
<tr>
<td>first degree relative, independently diagnosed with NF1</td>
</tr>
</tbody>
</table>

* Café-au-lait
Gigantic plexiform neurofibroma of lower back & leg

Segmental neurofibromata localised to dermatomes of right arm

Plexiform neurofibroma

Involving the face

Gigantic plexiform neurofibroma of lower back & leg

CT chest

Giant plexiform neurofibroma involving upper mediastinum & right side of chest

Neurofibroma in NF1 compressing cervical cord & nerve roots

Clawing, wasting & weakness of hands

Figure 18.1 Clinical features NF type 1
NEUROFIBROMATOSIS TYPE 2

Neurofibromatosis type 2 is a much rarer autosomal dominant disorder affecting about 1 in 50,000 due to a defect in the NF2 gene (merlin) on chromosome 22. It is characterised by few skin manifestations and the development of intracranial tumours, acoustic neuromas (vestibular Schwannoma) (Fig. 18.2) and meningiomas; see diagnostic criteria (Table 18.3). Deafness due to an acoustic neuroma involving the eighth cranial nerve is the main clinical presentation of type 2. This is usually accompanied by tinnitus, vertigo, ataxia, facial numbness and weakness. The clinical features at presentation are usually unilateral although the acoustic neuromas are commonly bilateral on neuroimaging. The diagnosis is confirmed by neuroimaging of the brain, usually MRI (Fig. 18.2). Management is either conservative by observation only or with deep X-ray therapy (DXT), or surgery for the tumours where possible. Genetic counselling is a very important part of management.

Table 18.3 Diagnostic criteria for NF2

<table>
<thead>
<tr>
<th>Criteria: a diagnosis of NF2 is made if one of the following is met.</th>
</tr>
</thead>
<tbody>
<tr>
<td>bilateral vestibular Schwannoma,</td>
</tr>
<tr>
<td>(either histologically or by MRI with contrast)</td>
</tr>
<tr>
<td>a parent, sibling or child with NF2 and either</td>
</tr>
<tr>
<td>a unilateral vestibular Schwannoma</td>
</tr>
<tr>
<td>or</td>
</tr>
<tr>
<td>2 or more of meningioma, glioma, Schwannoma,</td>
</tr>
<tr>
<td>posterior sub capsular lenticular opacities,</td>
</tr>
<tr>
<td>cerebral calcifications</td>
</tr>
<tr>
<td>multiple meningiomas (2 or more) and one or more of glioma, Schwannoma,</td>
</tr>
<tr>
<td>posterior sub capsular lenticular opacities, cerebral calcifications</td>
</tr>
</tbody>
</table>

MRI brain

Unilateral Schwannoma (right sided)

Figure 18.2 NF type 2
TUBEROUS SCLEROSIS

This is an autosomal dominant condition, due to mutations in either TSC1 on chromosome 9q (hamartin) or TSC2 on chromosome 16p (tuberin) with a prevalence of 1/15,000. Its frequency is not known in Africa but is most probably the same. About 60% of cases are due to new mutations. The main clinical features are the characteristic facial angiofibromata or adenoma sebaceum lesions on the cheeks and nose (Fig. 18.3), in combination with a history of epilepsy. There may be associated cognitive impairment. Additional skin manifestations include ash leaf hypopigmented macular type patches and the shagreen patch, a 1-10cm patch of orange peel like sub epidermal fibrosis found most often over the lumbar sacral area and subungual fibromas. CT shows a characteristic pattern of paraventricular subependymal calcified nodules or tuberi. Complications include tumours in the brain, hamartoma (Fig. 18.3) and astrocytoma. There are frequently other affected family members, most commonly siblings. Epilepsy may be difficult to control.

STURGE WEBER SYNDROME

This is an uncommon sporadic disorder affecting 1/50,000 in high income countries. It is a neurocutaneous syndrome characterized by a port wine staining affecting one half of the face (Fig. 18.4) usually in a V1 distribution and associated neurological abnormalities. The defining characteristic of the syndrome is an underlying intracranial vascular abnormality in the leptomeninges affecting the cortical regions of the hemispheres. The syndrome includes
seizures, glaucoma, headaches, behavioural problems and stroke like episodes. It has its onset usually in early childhood and is usually progressive. However the clinical course is highly variable and it is important to note that not all children or adults with the characteristic port wine facial staining have the syndrome. Neuroimaging, usually CT confirms the presence of intracerebral calcifications affecting the parietal or occipital lobes on the affected side but they can be generalised. Management is largely symptomatic and supportive.

**SPINOCEPHELLAR DISORDERS**

These represent a wide but rare group of disorders with progressive cerebellar degeneration in combination with other neurological findings. Friedreich's ataxia is one of the main early onset ataxias.

**FRIEDEICH'S ATAXIA**

Friedreich's ataxia is an autosomal recessive condition caused by mutations in the *FDRA* gene (frataxin) on chromosome 9, mostly trinucleotide (GAA) repeat expansions (67–1700). It affects 1/50,000 with its onset usually in young persons under the age of 20 years (average 15.5 years with a range of 2-51 years). The severity of the disease depends on the number of abnormal trinucleotide repeats. The disease is characterized by progressive degeneration of the main cerebellar tracts with involvement of the corticospinal and posterior columns. The main clinical feature is gait ataxia which progressively worsens and may be accompanied by pyramidal findings and peripheral neuropathy (absent ankle jerks). Other less frequent findings include optic atrophy and deafness. There may be a scoliosis, pes cavus, diabetes mellitus and an associated cardiomyopathy as evidenced by widespread T inversion on ECG.

There is no treatment for the underlying genetic condition and management is mainly supportive and treatment of complications. The differential diagnosis includes the other hereditary cerebellar ataxias which are mainly the later onset type (>20 yrs) and are mostly
autosomal dominant, mostly due to CAG repeat expansions and often characterized by anticipation. These may have associated spasticity, parkinsonism, neuropathy and retinopathy. A rare form of familial autosomal recessive isolated vitamin E deficiency is clinically very similar to Friedreich's ataxia and responds to high doses of vitamin E orally.

**INHERITED NEUROPATHIES**

These are also called the hereditary motor sensory neuropathies (HMSN). Charcot-Marie-Tooth disease (CMT1 = HMSN1) or peroneal muscular atrophy is the most common example in clinical practice. It is an autosomal dominant disorder, mostly due to 1, 5 Mb duplication, involving the \textit{PMP22} gene on chromosome 17p. It affects about 1/3000 and the age of awareness of the disorder ranges from childhood to middle age, although it is already established in childhood but is subclinical. Patients present with a chronic distal wasting of the lower limbs (Fig. 18.5) which progresses very slowly over many years. Typically there is marked wasting of the calf and distal thigh muscles with bilateral pes cavus (high arched feet with clawed toes), reflexes are lost as may be distal sensation. When wasting is severe the leg is said to resemble an inverted champagne bottle with a long neck. This may be accompanied by wasting of forearms and clawing of the hands in about a third of patients (Fig. 18.5). The level of disability is less than expected for the degree of wasting.

There is no specific treatment for inherited neuropathies. Nerve conduction studies show severe slowing of motor conduction velocities consistent with neuropathy. The differential diagnosis includes other long standing neuropathies including leprosy and less common forms of hereditary neuropathies. These rarer forms of hereditary neuropathies may be accompanied by signs of spastic paraparesis, deafness, optic atrophy and retinitis pigmentosa.

![Characteristic wasting of the legs](image1)

![Clawing of hands](image2)

**Figure 18.5** Charcot-Marie-Tooth disease

**HUNTINGTON’S DISEASE (HD)**

This is an autosomal dominant inherited neurodegenerative disorder, affecting particularly the caudate nucleus and presenting in middle age with choreaform movements, progressive dementia and psychiatric symptoms. There is usually a positive family history. It affects about 1 in 10,000 persons and the causative gene lies on chromosome 4. It is an example of
a trinucleotide repeat disorder with affected patients always having more than 36 cytosine-
adenosine-guanosine (CAG) repeats. The normal number of repeats is <30, intermediate
is 30-35, HD with reduced penetrance 36-39, and >39 in HD. The length of the repeats
predicts the onset of the disease, the greater the number of repeats the earlier the onset and
vice versa. Juvenile HD, characterized by rigidity rather than the chorea, is almost invariably
paternally inherited with repeat sizes of 60 or more. Early features of HD include psychiatric
and behavioural problems, characteristic fidgetiness, chorea and loss of intellectual function.
The symptoms typically start insidiously in middle age at around the 4th and 5th decade and
progress relentlessly to death within 15-20 years.

The diagnosis can be confirmed by diagnostic genetic testing, if available. Concerned relatives
at risk need to be counselled carefully before presymptomatic or predictive DNA testing is
performed. There is no effective treatment but the chorea and the anxiety may respond to
treatment early on in the disease. If the patient’s chorea is symptomatic tetrabenazine can be
effective but parkinsonism and depression are adverse effects. Benzodiazepines can be used for
anxiety and low dose haloperidol (0.5 mg bd) for aggression.

OTHER HEREDITARY NEUROLOGICAL DISORDERS

Muscular disorders
The main inherited myopathies are the dystrophies, Duchenne’s (DMD), Becker’s (BMD),
limb girdle (LGMD), facioscapulohumeral (FSHD) and myotonic dystrophy. These are
presented in chapter 13.

HEREDITARY SPASTIC PARAPARESIS (HSP)

This is an uncommon form of hereditary spastic paraparesis that usually follows an inheritance
pattern of autosomal dominance and less frequently recessive and X-linked. Several genetic
mutations occur involving over 20 different loci on different chromosomes with the spasmin
gene on chromosome 2p22 accounting for 40-50% of cases. Two main age groups are affected,
the more common one <35 yrs and the other with later onset (40-60 yrs) although the onset
can be at any age. The time course is usually one of slow progression over many years.

The most common clinical phenotype is usually that of a slowly progressive spastic paraparesis
beginning in childhood or teens characterized by hyperreflexia and up going toes with increasing
difficulty in walking. If it occurs in childhood there may be pes cavus or arched feet coupled
with tightening of the calf muscles which may result in heel-toe walking. Bladder and bowel
function are not usually directly affected. The upper limbs are variably affected. HSP can occur
in conjunction with other neurological abnormalities. These include cerebellar, optic atrophy,
peripheral neuropathy, ocular palsies, macular degeneration and retardation and dementia.

The differential diagnosis includes the main causes of chronic spastic paraparesis in Africa
including cord compression, primary lateral sclerosis, Konzo and HTLV-1. Management is by
genetic counselling and the paraplegia measures already outlined in chapter 10.
WILSON'S DISEASE

This is a rare autosomal recessive disorder of copper metabolism which affects mainly teenagers and young adults. It occurs with a frequency of between 1/50-100,000. It is characterized by the accumulation of copper in various organs of the body including the liver and brain. This is caused by a deficiency of caeruloplasmin a copper transporting protein in the blood. In the brain, it chiefly affects the basal ganglia resulting in a range of movement disorders including tremor, chorea, dystonia and parkinsonism. Diagnosis clinically is by finding evidence of cirrhosis in the liver or deposition of copper on the cornea called the Kayser-Fleisher ring. This may need a slit lamp examination. In the serum the caeruloplasmin level is low and copper level high. Treatment is with copper chelating drugs penicillamine and a low copper diet.

Key points

- hereditary neurological disorders are uncommon but cause serious long-term disability
- follow genetic principles of inheritance: autosomal dominance, recessive & X-linked inheritance
- often start in childhood or during teenage years & other family members are affected
- no effective treatment for most hereditary neurological disorders
- genetic counselling is very important

Selected references


