Learning difficulties have a very significant effect on individuals and on society. The affected individual will have difficulties in thinking, acquisition, and processing of new information and knowledge. As a result of these difficulties many individuals require additional care, education, and medical services. In some cases affected individuals will never achieve personal independence and the need for care will persist throughout their lifetime.

In the UK the term learning difficulty (or learning difficulties) is now preferred to older terms such as mental handicap or mental retardation. The term learning disorder is used slightly differently in the USA where it usually refers to specific learning difficulties such as dyslexia.

Learning difficulty is not a specific diagnosis—it refers to a collection of disorders in all of which impaired cognitive functioning is a common feature. This review will briefly discuss the causes of learning difficulty and will give guidance as to appropriate investigation of individuals who present with learning difficulty. It will also highlight some of the issues in management of the learning difficulties, particularly at the transition between paediatric services and adult learning disability services.

DEFINITIONS

Learning difficulties are defined on the basis of IQ (intelligence quotient). Only those individuals who score below 70 on a standardised IQ test are defined as having a learning difficulty. The normal IQ is considered to be over 85 and individuals with an IQ of between 71 and 84 are often described as having borderline intellectual functioning.

Learning difficulties are usually defined, on the basis of IQ score, as mild (IQ 50–70) or severe (IQ < 50). The severe category is often further subdivided into:

- moderate IQ 36–49
- severe IQ 20–35
- profound IQ < 20.

EPIDEMIOLOGY

Incidence and prevalence figures for learning difficulties vary throughout the world and within social class. The prevalence of mild learning difficulties is higher in developing countries than developed countries and this is thought to reflect poor socioeconomic conditions. The overall incidence of mild and severe learning difficulty in Western countries is around 8 per 1000, although this figure varies depending on the method of ascertainment with population based studies yielding higher rates. For example, in a one year cohort of Norwegian children followed until 14 years of age the overall prevalence of children with IQ < 70 was 11.9 per 1000.

Mild learning difficulty is approximately twice as common as severe learning difficulty, but the prevalence changes with age. Thus, although rates of severe learning difficulty are stable from about 3 years of age (because of the fact that it is usually recognised early), the rates of mild learning difficulty increase throughout the school years as more subtle difficulties become apparent.

It is well recognised that learning difficulty is more common in boys than girls with ratios varying between 3:1 and 1.9:1. This is mainly explained by the occurrence of specific X linked conditions (such as fragile X syndrome) in boys.

AETIOLOGY

There is a very wide range of conditions that may lead to learning difficulties. These include numerous medical conditions, both congenital and acquired, and social and environmental factors. The relative frequency of these various factors varies with the severity of the learning difficulty and with the socioeconomic background.

Aetiology is usually far more easy to establish in individuals with severe learning difficulty than in those with only mild learning difficulty or borderline intellectual functioning.
Mild
In this group the aetiologial factors are often prenatal but environmental influences play an important role. Despite careful assessment of history, clinical examination, and appropriate investigation, the aetiology will remain obscure in approximately 50% of affected individuals.

Most studies of aetiology in this group demonstrate that specific diagnostic entities are relatively rarely identified. In many cases the diagnosis of aetiology simply rests on the identification of risk factors. In a population based study of Norwegian children born between 1980 and 1985 there were 99 children with mild learning difficulties. In 68% of these children there was considered to be a biological basis for the learning difficulties, of which 51% were prenatal, 5% perinatal, and 1% postnatal in origin. The remaining 11% were undetermined in the timing of the insult which led to the learning difficulty. A small proportion of the children were found to have a single gene defect. In an earlier Swedish study alcohol fetopathy was found to be responsible for one third of all prenatally derived mild learning difficulties. Other important prenatal (and potentially preventable) factors include maternal heroin and cocaine abuse, and HIV encephalopathy.

The evidence of prenatal insult may be very subtle. Although the presence of frank dysmorphism makes the recognition of a prenatal aetiology easy, more subtle abnormalities require careful examination. Several studies have demonstrated the importance of abnormal dermatoglyphics as markers of prenatal disturbance in learning difficulties of unknown aetiology. Increased arches, a simple fingerprint pattern, and increased radial loops (which is an unusual pattern) have all been found in children, particularly boys, with learning difficulty more commonly than in healthy controls. A significant increase in abnormal flexion creases has also been identified in individuals with learning difficulty. In some cases these subtle abnormalities may be the only indicator of the cause of the learning disability.

Recently there has been the suggestion that in prepubertal males with mild learning difficulty of unknown aetiology Klinefelter syndrome may be the single most common cause, even in the absence of dysmorphic features. It should be noted, however, that the incidence of learning difficulty following prenatal diagnosis of Klinefelter syndrome is significantly lower than in boys identified postnatally.

Perinatal risk factors for mild learning difficulty include low birthweight, prematurity (gestational age < 32 weeks) and persistently low five minute Apgar scores. These factors do not imply a cause and effect relationship but in some cases may simply reflect the impact of prenatally operating factors.

Early onset epilepsies, acquired head trauma (especially non-accidental injury), and non-convulsive status epilepticus may result in mild learning difficulty, although these insults often lead to more severe learning difficulty.

It is likely that many of the children with mild learning difficulty who have no identifiable risk factors represent a continuum of the normal population.

Severe
Biological factors account for a significantly greater proportion of severe learning difficulty. In the Norwegian study of Strommë biological factors were responsible for 96% of cases of severe learning difficulty. This figure is lower in some other studies with significant numbers of children remaining undiagnosed despite appropriate investigation.

Table 1 gives a breakdown of many of the causes of severe learning difficulty. In this group of patients prenatal factors account for the majority of the identified causes. In the Norwegian study the aetiology was prenatal in 70%, perinatal in only 4%, and postnatal in 5%. In 18% the timing could not be ascertained.

Chromosomal abnormalities
The single most common cause of learning difficulty is trisomy 21 (Down syndrome). The condition occurs on average in 1:650 births, although there is a strong association with maternal age. In women over 45 years the incidence is 1:54. There is also a tendency to high incidence in infants born to very young mothers.

In most cases Down syndrome occurs as a result of non-disjunction leading to the presence of a third chromosome 21 in cells. However, in approximately 8% of cases there is translocation of a part of chromosome 21 onto another chromosome. It is not known how the presence of the extra chromosomal material leads to the clinical syndrome.

The clinical features of Down syndrome are very typical and are outlined in table 2. Other trisomy syndromes such as Edward syndrome (trisomy 18), Patau syndrome (trisomy 13),

<table>
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<th>Timing of insult</th>
<th>Aetiological factor</th>
<th>Examples</th>
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<tr>
<td>Prenatal</td>
<td>Chromosomal abnormalities (account for ~50% cases)</td>
<td>Down syndrome (trisomy 21); Angelman syndrome (15q11.2-12)</td>
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<td>Inborn errors of metabolism</td>
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<td>Genetic disorders (including X linked)</td>
<td>Fragile X syndrome; Rett syndrome</td>
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<td>Intrauterine infection</td>
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<td>Intrauterine toxins</td>
<td>Alcohol, drugs—AEDs</td>
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<td>Recognisable syndromes (including neurocutaneous)</td>
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<td>Cerebral malformations</td>
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<td>Others</td>
<td>Congenital hypothyroidism; Duchenne muscular dystrophy</td>
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<tr>
<td>Perinatal</td>
<td>Birth asphyxia</td>
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<td>Neonatal meningoencephalitis</td>
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<td>Postnatal</td>
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<td>Trauma</td>
<td>Non-accidental injury; RTA</td>
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<tr>
<td></td>
<td>Epileptic encephalopathies</td>
<td>West syndrome, Lennox Gastaut syndrome</td>
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</table>

AEDs, antiepileptic drugs; CMV, cytomegalovirus; RTA, road traffic accident.
and trisomy 8 are much less common than Down syndrome and are easily recognised by their clinical features.

Other chromosomal disorders account for a significant proportion of learning difficulties. These include deletion syndromes such as Angelman syndrome (15q11.2-12), Prader-Willi syndrome (15q11-13), Cri-du-Chat syndrome (5p-), etc. Many other minor deletion syndromes have been described as well as duplications, ring chromosomes, etc.

**Sub-telomeric defects**

Screening for sub-telomeric chromosome defects using FISH (fluorescent in situ hybridisation) is now available in some centres. In selected series of children up to 7.4% with moderate to severe learning difficulty and 0.5% with mild learning difficulty have been shown to have sub-telomeric chromosome rearrangements. The technique is costly and time consuming and clinical indicators are therefore required when making a request for this investigation. There is an increased chance of identifying such defects in the presence of prenatal growth failure, where there is a family history of learning difficulty and where there are dysmorphic features. The pickup rate of these defects in unselected series is much lower.

**X linked learning difficulty**

Although the fragile X syndrome is the most common X linked cause of learning difficulty, several other X linked causes of learning difficulty have been described. Many of these are heterogeneous and linkages to various regions on the X chromosome have been described.

Others, such as the Coffin-Lowry syndrome, are well described. In this condition there are clearly recognisable clinical features—the condition affects males and is characterised by short stature, a coarse face with prominent forehead, hypertelorism, downsloping palpebral fissures, thick lips, a thick nasal septum with anteverted nares, and irregular or missing teeth. Other features include typically large and soft hands with lax skin and tapering fingers, sensorineural deafness, seizures, and cardiac disease. In 50% of patients this condition is shown to be caused by loss of function mutations affecting the gene which encodes for growth factor induced protein kinase ribosomal S6 kinase with over 80 mutations currently described.

There is an increased risk of learning difficulty in boys with Duchenne muscular dystrophy. The mean IQ of boys with Duchenne muscular dystrophy is 85 with a range from 40–130. Approximately 20–30% of affected boys will have an IQ of less than 70.

Recently there has been interest in the association between mutations in C-terminal domain of the MECP2 gene (which causes Rett syndrome in girls) and learning difficulties in males. The significance of these findings is still under review and a recent French study demonstrated that these mutations are also to be seen in healthy, non-learning disabled individuals.

In general the more complex X chromosome disorders (such as males with three or more X chromosomes) are likely to be associated with more severe learning difficulties.

Rett syndrome is an increasingly recognised cause of learning difficulty in females. The clinical picture is very characteristic and follows a pattern of early developmental stagnation with failure of head growth from approximately 6–18 months followed by a rapid neurological regression with the development of an autistic picture and loss of useful hand function. Thereafter there is a stable period over many years with severe learning difficulties, odd hand stereotypes, abnormal respiratory pattern, seizures, and the development of scoliosis. In early adolescence and adult life there is a progressive motor disorder with mixed upper and lower motor neurone findings, progressive scoliosis, and loss of ambulation. In 80% of affected girls a mutation in the MECP2 gene has been identified.

**Fragile X syndrome**

This is the second most common cause of learning difficulty. The disorder was first recognised by the presence of a fragile site on the X chromosome when cultured in a folate deficient medium. It is now recognised that the syndrome is caused by a large methylated repeat of a CGG repeat in the FMR1 gene. This results in a loss of expression of FMRP which is an RNA binding protein. It is suggested that FMRP acts as a regulator of an mRNA transport or translation that is important in synaptic maturation and function. The affected male infant is the result of amplification of the (usually) asymptomatic pre-mutation carried by his mother.

The clinical phenotype is more easily recognised after puberty than in the younger child. In the early years the only clinical features may be the learning difficulty which is often in the mild/moderate range. The pre-pubertal male may have a large head, large ears, a high arched palate, and joint hypermobility. After puberty the classical features of a long face with prominent jaw, large ears, and macro-orchidism are more readily appreciated. The learning difficulty tends to become more severe with age.

Cognitively there is often a typical pattern of difficulties with specific deficits in attention, speech, language, and social communication. Frank autism is seen in approximately one quarter of cases.

In carrier females up to a third may have learning difficulty, usually in the mild range. They may also show facial features of fragile X and some have psychiatric disorders without associated learning difficulty.

**Cerebral malformation**

Cerebral malformation is defined as any morphological abnormality of the brain that dates to the embryonic or fetal period regardless of mechanism. There are numerous recognised causes for cerebral malformation including environmental factors (for example, intrauterine infections or toxins), genetic factors, etc. In the majority a specific aetiology
Neurocutaneous syndromes

There are a number of disorders which affect both the nervous system and skin, probably because of common embryological factors. Most present in early life and are easily recognisable, although in some clinical manifestations may not become apparent until adult life. Many of these disorders involve other systems in the body than simply skin or CNS. Learning difficulty is a well recognised feature in neurofibromatosis type 1, tuberous sclerosis, linear sebaceous naevus syndrome, incontinentia pigmenti, and hypomelanosis of Ito, although there are many other rare disorders which have been described. In a review such as this it is not possible to discuss all the recognised neurocutaneous syndromes and details are found in many neurology and paediatric neurology textbooks.

Tuberous sclerosis (TS) is the most common of the neurocutaneous disorders. It is truly a multisystem disease with abnormalities found in skin, eyes, kidneys, liver, heart, and brain. Two mutations have been associated with the disease: TSC1 lies on chromosome 9 and produces a protein known as hamartin; and TSC2 lies on chromosome 16 and produces a protein tuberin. These proteins are probably responsible for regulation of cell proliferation.

Clinically the condition is recognised by the typical cutaneous lesions—hypopigmented macules (fig 1), flat forehead fibromata, adenoma sebaceous, shagreen patches, and subungual fibromata. Around 47% of individuals with TS have learning difficulties. Learning difficulty is seen only in those individuals who suffered seizures in the first two years of life. On magnetic resonance imaging the typical features of subependymal tubers (fig 2), cortical tubers, and giant cell astrocytoma can be readily visualised.

Perinatal factors

Although perinatal factors account for only a small proportion of cases of severe learning difficulty they are important because in some cases they are preventable. The majority of perinatal insults which result in learning difficulty also lead to other significant neurological disorders such as cerebral palsy.

Birth asphyxia is a very important cause of learning difficulty and cerebral palsy although the majority of infants who are asphyxiated at birth will recover without permanent neurological disability. However, the combination of significant birth asphyxia (evidenced by a persistently low Apgar score at five minutes after birth and acidosis) and a moderate or severe neonatal hypoxic ischaemic encephalopathy has a significant predictive value for long term damage.

Other important perinatal factors include prematurity and low birthweight, birth trauma such as intracranial haemorrhage, and neonatal CNS infection (bacterial meningoencephalitis, viral encephalitis).

Postnatal factors

Any insult occurring to the developing brain after birth may result in learning difficulty although, as with perinatal factors, this is often accompanied by other acquired neurological disabilities such as cerebral palsy.

As would be expected, generalised hypoxic ischaemic insults often lead to cerebral palsy, cortical visual agnosia, microcephaly, and learning difficulty. In some cases the early motor and visual manifestations become less prominent with time and the only remaining disability is a learning difficulty. Such hypoxic ischaemic damage may follow so-called “near miss cot death”, attempted smothering by mothers, drowning accidents, etc, or may occur during surgical procedures, particularly correction of complex congenital heart disease.

Other important causes include CNS infection and head trauma (both accidental and non-accidental). It is increasingly recognised that there is a high incidence of permanent neurodevelopmental disability following inflicted head injury probably because of the combination of traumatic and hypoxic ischaemic damage which occurs.

Permanent neurodevelopmental disability is well recognised in children with early onset epilepsies. Although the association of severe early epileptic encephalopathies such as West syndrome, severe myoclonic epilepsy of infancy (Dravet syndrome), and Lennox Gastaut syndrome with permanent cognitive, motor, and sensory disability is well known, it is also recognised that such difficulties may follow focal epilepsies with onset at less than 24 months. It is possible that early surgical treatment of these epilepsies may have a beneficial effect on outcome.

In global terms malnutrition is a very important cause of learning difficulty.

INVESTIGATION

It is clear from the discussion above that there is a wide range of possible causes for learning difficulty. It is also clear that not
all patients require all investigations to be performed and investigation should be targeted to the clinical situation. For neurologists the task is often easier than for paediatricians/ paediatric neurologists as many evolutionary conditions are apparent and most metabolic diseases will have become manifest during childhood. It is sensible to consider both medical and neuropsychological investigation.

Medical
In all patients with learning difficulty the starting point is with a careful history. This should include questions about the pregnancy, especially about maternal health and exposure to environmental toxins such as drugs, alcohol, x rays, etc. Birth history is important and attention should be paid to whether delivery occurred at full term, whether there were any problems with the birth itself, and to neonatal well being. In general the infant who was discharged home without entering the special care baby unit is unlikely to have experienced a significant perinatal neurological insult.

Thorough clinical examination is essential. This should include a careful examination of the skin to identify any markers of a neurocutaneous syndrome. It is also necessary to look for dysmorphic features which may suggest a chromosomal or syndromic cause for the learning difficulty. It is worth remembering that the dysmorphic features may be very subtle.

When an individual reaches the age that they are transferred to the adult services many of the potential causes of learning difficulty will be evident—for example, Duchenne muscular dystrophy, most inborn errors of metabolism. Many other causes, such as phenylketonuria, congenital hypothyroidism, etc, will have been excluded by routine screening in the newborn period. However, care should be taken to identify the individual born in developing countries where routine neonatal screening does not occur. A classical error is to fail to recognise the familial microcephaly and learning difficulty of children born to a mother with untreated phenylketonuria. These children will have normal phenylalanine concentrations on neonatal screening, as the neurological damage occurs as a result of exposure to high concentrations of phenylalanine in utero.

The following investigation is appropriate for the undiagnosed patient with learning difficulty.

**Mild learning difficulty**
- History
- Examination (with attention to skin, dysmorphic features)
- Chromosomes
- DNA for fragile X (in males)
- Sub-telomeric FISH (if appropriate on clinical assessment)
- EEG (if clinical suspicion)

**Severe learning difficulty**
- History
- Examination (with attention to skin, dysmorphic features)
- Ophthalmology review
- Chromosomes
- DNA for fragile X
- Sub-telomeric FISH (if clinically appropriate)
- Magnetic resonance imaging

Other investigations may be required depending on the clinical presentation.

**Neuropsychological**
The vast majority of adults with learning difficulty will have undergone appropriate neuropsychological testing during childhood. It is important to remember that some of these individuals may have been labelled as having mild/moderate difficulties in early life but now present with severe learning difficulty. This is rarely due to a progressive neurological disorder but simply reflects the fact that early neuropsychological testing cannot be as accurate as later testing because of the effects of maturation and the relatively less sophisticated function which can be tested in early childhood.

Further neuropsychological examination may be warranted, however, if there are concerns about a fluctuating deficit or real concerns about cognitive decline. Occasionally patients labelled as having a general learning difficulty in early life are found to have only specific difficulties on further testing. Thus, it is important to have an open mind when meeting people with learning difficulty for the first time.

**SPECIFIC LEARNING DIFFICULTIES**
In the early 20th century it was believed that early damage to the brain often resulted in a picture of impaired attention and hyperactivity. The converse of this was that this picture was commonly the result of early brain damage. Subsequently this view has been successfully challenged and it is now recognised that most children with attentional or specific learning difficulties do not have any diagnosable brain injury.

There is no doubt that there is an over representation of attentional difficulties in children with significant neurodevelopmental disorders, particularly epilepsy. However, the presence of attentional difficulties does not signify the presence of a neurological disorder and medical investigation of the cause of these difficulties (in the absence of strong clinical indicators) is rarely of value.

Specific learning difficulties such as dyslexia and dyspraxia are very rarely caused by specific neurological disorders and medical investigation is not warranted.

**ASSOCIATED DISABILITIES**
Learning difficulty is often associated with diffuse and widespread neurological dysfunction. It is not surprising, therefore, that there is a strong association with other neurological deficits.
Epilepsy is strongly correlated with learning difficulty. In a Danish population study the incidence of epilepsy in all people with learning difficulty was 20% and this rose to 50% in the most severely affected individuals. Other common associations are cerebral palsy, which affects approximately one fifth of individuals with severe learning difficulty, and psychiatric disorders which affect over half of individuals with learning difficulty.

The most common psychiatric disorders are hyperkinesia and autism. Autism is approximately 100 times more common in individuals with learning difficulty than in individuals with normal intelligence. Other minor behavioural abnormalities such as motor stereotypes, pica, etc, are over represented in the learning disabled population.

Frank neurological disorders such as severe visual and/or hearing impairment and hydrocephalus are found in 5–15% of individuals with severe learning difficulty, but are much less common in individuals with mild learning difficulty.

MANAGEMENT

For the vast majority of conditions which cause learning difficulty no cure is available. However, the clinician must be alert to the rare situation in which non-convulsive status epilepticus is responsible for or exacerbating learning difficulty, as successful treatment of the non-convulsive status epilepticus will reverse the problem.

For many conditions prevention is possible either by immunisation (for example, congenital rubella), screening, and appropriate treatment (for example, hypothyroidism) or by appropriate economic intervention (for example, malnutrition).

In most cases the management is geared to diagnosis, both of the problem and if possible the cause, appropriate genetic counselling, and to support (medical, educational, and social). Medical intervention usually involves dealing with complications of the learning difficulty and coordination of appropriate support services. In adult practice much of this role is provided by the learning disability service, but the neurologist may be involved in management of epilepsy and other associated neurological disorders.

Transition

The transition from paediatric to adult services is one fraught with difficulties. Although there are statutory processes which deal with the move from a primarily educational provision to provision of support by social services, the medical transition is often less clear. In many areas the learning disability service does not intervene until the age of 18 years while paediatric services finish at 16 years. In this situation the neurologist may be faced with providing a neurological service to this population. Progress in the area of transition requires considerable further work.

REGRESSION

Although most patients with learning difficulty who reach the neurologist will have a stable disability, a small subgroup may present with a late deterioration. The first task of the neurologist will be to determine whether this is a real or apparent cognitive decline. In this situation there is often valuable information available in the form of previous neuropsychological assessment, although this may have been performed many years earlier. There will also be valuable information available from educational records and this can be compared with an updated neuropsychological assessment.

In many cases the apparent decline will be caused by non-neurological factors such as psychiatric disorder. In other cases there will be no cognitive deterioration but rather a cognitive stagnation or slowing. Rarely there will be frank cognitive regression or dementia.

In the population with learning difficulty the approach to cognitive regression will be very much the same as for the non-learning disabled population. However, a number of specific disorders can be recognised. These include slowly progressive neurological disorders such as Pelizaeus Merzbacher disease (which is X linked) or Alexander disease. These are both leucodystrophies in which the course may be so slowly progressive that in childhood they simply present as a cerebral palsy. In both of these cases the findings of a leuco-dystrophy on magnetic resonance imaging will suggest the diagnosis.

Some mitochondrial disease may present in childhood without any progressive features and thus the metabolic nature of the problem may not be recognised. The emergence of typical clinical features such as dystonia or epilepsy, especially with other organ involvement, with progressive neurological dysfunction in adolescence or adult life will prompt further assessment with magnetic resonance imaging, plasma lactate, CSF lactate, and specific enzyme studies.

In individuals with epilepsy non-convulsive status epilepticus may present with cognitive or behavioural deterioration without much else in the way of clinical signs. Progressive hydrocephalus may present late with cognitive decline. In Down syndrome early dementia is common.

PROGNOSIS

The prognosis for individuals with learning difficulty is variable and depends on a number of factors including aetiology, severity of the learning difficulty, and the presence or absence of associated medical and behavioural problems. In no cases is the learning difficulty likely to become less severe with age and in some conditions (as discussed above) there may be cognitive decline in adult life.

Individuals with severe learning difficulty (IQ < 35) in school years are likely to remain dependent on parents or carers throughout their lives. Some individuals with moderate learning difficulty may be able to live independently, but this depends on many factors including social integration. In all cases there will be ongoing cognitive difficulties.

It is well recognised that there is an increased risk of premature mortality in individuals with learning difficulties. The risks are greatest in those individuals who are most severely impaired, particularly those who have severe motor impairments. This is because the most immobile and severely disabled individuals are at the highest risk of respiratory infection, and this is the most common cause of early death in this population.

REFERENCES


