may present in adults with a multisystem syndrome including cerebellar dysfunction.[4-6] Cholestanolosis, a rare autosomal recessive disorder caused by defective bile salt metabolism, causes ataxia, dementia, spasticity, peripheral neuropathy, cataract, and tendon xanthomas in the second decade of life. Treatment with chenodeoxycholic acid appears to improve neurological function.[7] Longstanding severe vitamin E deficiency causes a syndrome of progressive ataxia, areflexia, and distal loss of vibration and position sense. This may occur secondary to acquired fat malabsorption and is the basis for the neurological syndrome associated with abetalipoproteinaemia.[8,9] Recently patients with isolated vitamin E deficiency, probably inherited as an autosomal recessive trait, have been reported.[10] Adequate doses of vitamin E stop the progression of neurological symptoms and lead to improvement in some cases.[8,9]

Degenerative ataxic disorders of unknown cause that begin in childhood or adolescence are nearly always genetically determined, and most are autosomal recessive. The commonest of these is Friedreich's ataxia, which usually first causes symptoms between 8 and 16 years. Its cardinal features are progressive ataxia of gait and the limbs, dysarthria, and areflexia; signs of pyramidal tract dysfunction and loss of vibration and joint position sense eventually appear in all patients. Scoliosis and electrocardiographic evidence of heart muscle disease occur in about 70% of cases of Friedreich's ataxia. Less common features include pes cavus, optic atrophy, distal wasting, and diabetes. On average patients lose the ability to walk 15 years after symptoms begin and die in their 40s and 50s.[2] The cause of Friedreich's ataxia remains unknown, and early reports suggesting deficiencies of the pyruvate dehydrogenase or mitochondrial malic enzymes have not been confirmed.[11-15] Efforts to localise the gene for the disease to a specific chromosomal region have so far excluded it from about half of the genome (S Chamberlain, personal communication).

When presented with adults with slowly progressive cerebellar dysfunction doctors must exclude hypothyroidism, alcoholism, and malignancy, although paraneoplastic cerebellar degeneration usually causes more acute illness. About one third of patients with degenerative ataxia developing over the age of 20 have similarly affected relatives, and inheritance is usually autosomal dominant. The pathological findings in late onset cerebellar degenerations are variable, but the syndrome of olivopontocerebellar atrophy (loss of cells in the pontine and olivary nuclei and also of the cerebellar Purkinje cells) is seen in at least half of familial and sporadic cases. There are nearly always accompanying degenerative changes in the basal ganglia, spinal cord, and peripheral nerves, so the term olivopontocerebellar atrophy is misleading and not a good diagnostic label.[16]

Most patients with late onset ataxia that is dominantly inherited do not have a pure cerebellar syndrome; commonly they also have features such as supranuclear ophthalmoplegia, optic atrophy pigmentary retinopathy, dementia, and extrapyramidal dysfunction.[2] Sporadic cases are clinically similar; the aetiology of their disorders is not known, but some probably represent fresh dominant mutation.[2] It has been suggested that leucocyte glutamate dehydrogenase activity is specifically reduced in some patients with olivopontocerebellar atrophy,[17,18] but a recent British study has not confirmed these observations (D Aubby *et al*, personal communication).

Most attempts at treating degenerative ataxias have given disappointing results, reflecting our incomplete knowledge of neurotransmitter function in the cerebellum and its connections.

γ-Aminobutyric acid appears to be the most important inhibitory neurotransmitter, but trials of agonists to γ-aminobutyric acid—such as sodium valproate, baclofen, and isoniazid—have failed to show functional benefit.[2,19] The same applies for cholinergic drugs.[19] Promising results using thyrotropin releasing hormone in treating ataxia have been reported from Japan; these observations need to be confirmed, but they suggest that noradrenergic input to the cerebellum is more important than previously realised.[20]

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Important new treatments for acute ischaemic stroke?

Three recent trials have suggested that glycerol,[1] naftidrofuryl,[2,3] and nimodipine[4] may reduce mortality[1,4] or morbidity[2,3] after acute ischaemic stroke. Treatment with glycerol reduced the odds of death within seven days by 68%,[1] and treatment with nimodipine reduced the odds within four weeks by 70%.[4] Although naftidrofuryl did not have a statistically significant effect on early death, the authors concluded that the observed reductions in morbidity were statistically and clinically significant.[2,3] All three trials were, however, small, including only 173,[1] 164,[4] and 89[2,3] patients. For this reason alone they do not provide evidence reliable enough to justify nationwide use of the treatments.[5]

Combining the results of several small trials that are individually uninformative with all other available methodologically sound trials in a formal statistical overview may

yield more useful results.[6,7] The technique of such overviews (or pooling) is simple and well described,[6] though there are pitfalls[7]; and restriction of the analysis to published data may overestimate the size of the treatment effect since positive studies are more likely to be published.

An overview analysis of the published randomised controlled trials of glycerol in acute stroke[1,8-14] shows that treatment reduces the odds of death within six weeks by about 36% (pooled relative odds 0·64, 95% confidence interval 0·42 to 0·96). An analysis of the results from the four trials that reported longer follow up[1,12-14] shows that treatment is associated with a non-significant reduction in the odds of death within four months to one year of 21% (pooled relative odds 0·79, 95% confidence interval 0·49 to 1·28). The confidence intervals are wide and include the possibility that glycerol reduces the odds of early death by only 4% and increases the odds of later death by 28%. An overview analysis of the two published studies of naftidrofuryl[2,3,15] shows that treatment is associated with a 29% reduction in the odds of death within three months but a 16% increase in the odds of remaining in hospital more than three months after the stroke. The confidence intervals were wide and naftidrofuryl could have important favourable effects on death and hospital discharge (reducing the odds by 64% and 35% respectively) or could equally have large adverse effects (increasing the odds by 40% and 107% respectively). Only one study of nimodipine in acute ischaemic stroke has been published[4] so an overview analysis is not possible, but the study had similarly wide confidence intervals—for death within four weeks the relative odds were 0·30 (95% confidence interval 0·10 to 0·88).

Any trial of an agent designed to ameliorate acute ischaemic stroke should not include patients with haemorrhagic stroke. Two trials have performed computed tomograms to exclude intracranial haemorrhage on every patient,[2,3,14] one on only a proportion of patients,[1] and the remainder on none or an unstated proportion. We cannot be sure that the treatment has been tested in the correct patients in trials that have not scanned all patients.

A more serious problem in all of the published trials is the quality of the data on morbidity in the survivors of acute stroke. While it is important to know whether treatment increases or reduces the chances of surviving a stroke, it is even more important to know whether treatment improves survival free of disability and dependency. None of the trials have reported their results in a way that allows assessment of this crucial measure of outcome; instead, some have used scales of neurological impairment such as the Mathew scale.[8-14] Unfortunately this scale does not measure handicap or activities of daily living, and neither the original nor the subsequent modifications have been shown to be reliable, repeatable, or valid. None of the trials used a simple valid measure of activities of daily living such as the Barthel index[16]; nor did they attempt to measure quality of life, which is surely important for the disabled survivor of a stroke.[16]

The patients in these studies had all been admitted to hospital with severe strokes and were at high risk of dying: one month case fatality rates in those allocated placebo were 50%,[1] 21%,[2] and 21%.[4] These results suggest that these strokes were more likely to be caused by large vessel occlusion than by small vessel disease resulting in lacunar infarction.[17,18] Lacunar infarctions may not respond to the same treatments as large vessel occlusions, and failure to differentiate large infarcts from lacunar infarcts may obscure important treatment effects.[17,18]

Further trials of these agents are clearly necessary. They need to be larger and confined to patients with cerebral infarction confirmed by computed tomography. The cerebral infarct should be categorised on the basis of clinical and computed tomography findings into the different subtypes of infarction. The trial results must include data on both early and late survival, on survival free of dependency, on handicap, and on quality of life measured with simple, reliable, and valid measuring scales.[16] At present there is inadequate evidence to support the use of glycerol, nimodipine, or naftidrofuryl when routinely treating patients with acute ischaemic stroke.

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Mortality in congestive heart failure: effects of vasodilator therapy

Congestive heart failure is a common condition with a poor prognosis. The principal determinant of prognosis is left ventricular function, and when this is severely depressed (causing dyspnoea at rest or on minimal exertion) over half the patients are dead within a year.[1] Diuretics are the first line treatment but, although these control fluid retention, they do not improve left ventricular function. Vasodilator drugs, on the other hand, improve left ventricular function by reducing afterload and are widely used in patients who still have symptoms after treatment with diuretics.

Activation of the renin-angiotensin system is a major factor in the development of the heart failure.[2,3] The angiotensin