

Sensory form of Guillain-Barré syndrome

Guillain-Barré syndrome, a clinical syndrome of rapidly progressive weakness attributable to polyradiculoneuropathy and reaching its nadir within 4 weeks, is now recognised to be due to any one of several pathological processes.¹ The commonest underlying pathological change in Europe and North America is acute inflammatory demyelinating polyradiculoneuropathy, which affects mainly the anterior spinal roots and motor nerve fibres and causes more weakness than sensory loss. The inflammation causes demyelination and, when severe, axonal degeneration as well. In parts of China, Japan, India, and central and South America the underlying abnormality is more commonly an acute motor axonal neuropathy, in which the primary autoimmune attack is directed against the axon. The classic syndrome includes weakness as part of the clinical picture. However, several related syndromes have come to be regarded as variants of Guillain-Barré syndrome even in the absence of weakness because overlap forms occur and the pathogenesis is considered to be a similar autoimmune attack on a peripheral antigen. The best known variant is the combination of ataxia, ophthalmoplegia, and areflexia described by Fisher in 1956.²

Shin J Oh and colleagues' description of eight cases of a sensory form of Guillain-Barré syndrome resolve a long-standing debate on whether such an entity exists.³ Cases of transient sensory neuropathy are not uncommon but their benign nature and the absence of histological information make it impossible to determine the underlying abnormality.⁴ When the sensory action potentials become unrecordable it is not possible to discover whether conduction block is due to axonal demyelination or degeneration. Oh and colleagues found strong neurophysiological evidence of demyelination affecting motor nerve fibres in seven cases and similar evidence affecting sensory nerve fibres in the eighth. These findings indicated a predominantly rather than purely sensory disorder. The underlying pathological process was presumably acute inflammatory demyelinating polyradiculoneuropathy. These investigators were sensitised to the possibility of the existence of this variant by their previous description of a predominantly sensory form of chronic inflammatory demyelinating polyradiculoneuropathy, which is also usually a predominantly motor disorder. Other features of their cases resembled classic Guillain-Barré syndrome. Five of the eight had preceding viral illnesses. In the four who had lumbar punctures at the time of the acute illness, the cerebrospinal fluid protein concentration was increased. All had a monophasic illness with complete recovery, some with and some without treatment.

Doctors must now add predominantly sensory acute inflammatory demyelinating polyradiculoneuropathy to the differential diagnosis of acute sensory neuropathy. Other causes are neuropathy due to diabetes mellitus and other metabolic causes, vitamin B12 deficiency, vasculitides, Sjögren's syndrome, sarcoidosis, HIV infection, Lyme disease, drug and chemical intoxication, an underlying carcinoma, and leprosy. The main difficulty will remain the distinction from acute idiopathic sensory neuronopathy, which is a pure sensory syndrome generally occurring without any antecedent illness.⁵ It may cause numbness, tingling, and ataxia due to large-fibre damage or painful paraesthesiae or both. The severity and natural history are variable. Although improvement may eventually occur, severe persistent disability is common. Whether treatment is helpful is not clear, but steroids are often used.⁵

Recognition of a predominantly sensory form of acute inflammatory demyelinating polyradiculoneuropathy raises

the challenge of identifying the antigen that focuses an autoimmune attack predominantly on the Schwann cells and myelin sheaths of sensory rather than motor axons. Progress has been made with identifying the antigenic target in Fisher's syndrome. In that disease antibodies to ganglioside GQ1b are almost always found. There is an approximate match between the location of GQ1b and the presumed sites of the lesions in Fisher's syndrome.⁶ In acute motor axonal neuropathy the situation is not yet so clear. Associations have been proposed with several different gangliosides.¹ In the Chinese cases there is an association with antibodies to ganglioside GD1a,⁷ and murine monoclonal antibodies to this antigen identify epitopes on motor but not sensory axons (Lunn M, Sheikh K, personal communication). A humoral or possibly T-cell-mediated immune response to a Schwann cell or myelin antigen is likely to be the cause of acute inflammatory demyelinating polyradiculoneuropathy. The existence of sensory as well as motor predominant forms of this disease suggests that sensory and motor axons differ in the epitopes that they present.

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Research in the EU: better times to come?

On Feb 21, 2001, the European Commission (EC) set out a proposal for the Sixth Framework Programme (FP6) for science research, which covers the period 2002–06.¹ FP6 is regarded as a major instrument in implementing the European research area (ERA), a concept launched last year to promote a knowledge-based economy and society.²

Previous framework programmes have been criticised for lack of coherence and continuity. FP5 (1998–2002) in particular is not highly regarded by scientists because of its tortuous application procedure, the lack of transparency in the evaluation of the applications, and lack of opportunity for open-ended, creative research. FP6, intended to make best use of Europe's research resources and to be fully open to EU candidate countries, will be somewhat different. As in FP5, existing problems (rather than emerging needs) in priority areas will be tackled through targeted research programmes (called "integrated projects") conducted by consortia of academic groups and private companies. However, novel structures, "networks of excellence", will be set up to promote research integration. Another new feature is that funds will be reserved to address emerging needs or scientific and technological breakthroughs. To structure and strengthen ERA, the EC plans chiefly to expand the mobility programme, to support

initiatives leading to the networking of national research programmes and their mutual opening-up to researchers from other EU countries, and to offer better access to research infrastructures. Funding will be allocated to identify the needs in, perform feasibility studies for, and cover up to 10% of the construction costs of new infrastructures. FP6 will also increase support of research conducted by small and medium sized enterprises, and help to initiate actions strengthening the social dimension of science (ethics, public awareness of science) and to make science more appealing to young people.

Several features of the proposed FP6 are very positive and testify to a vision that has been missing in the past. The networking and the mutual opening-up of national programmes will certainly increase their impact and their outcome. The facilitation of transnational access and the coordination of the activities across nations may help to reduce the current deficit of research infrastructures in Europe.³ But the FP6 proposal is at this stage only a political document that will serve as a matrix for the preparation of the detailed work programme. The problem is that negotiations, now underway, during its passage through the European Parliament and Council, are based on a document that is in many parts abstract and not explicit about how the proposals will be implemented.

According to the EC, greater efficiency should result from focusing a critical mass of expertise on a limited number of projects of longer duration. This notion underlies the proposal for networks of excellence around joint programmes of activities based on priority themes. In contrast to FP5 projects, network participants will be accorded both flexibility in research topic and autonomy to adapt their programme according to research progress. Additionally, new partners may be taken on board in the course of the project. Participants will have to integrate their activities, exchange personnel, make intensive use of communication tools, and pay attention to knowledge transfer and exploitation. There will be, however, no request for pre-defined results, the notorious "deliverables" of FP5. Each network of excellence will be granted several millions of euro per annum, compared with an average 1.5 million euro per project under FP5.

Although the advantage of large versus small projects is a matter of debate, the networks of excellence may serve as a suitable instrument for promoting basic research. The EC insists that FP6 will promote networks of excellence and not centres of excellence. Nevertheless, the definition of, and the criteria for, excellence remain crucial. Furthermore, networking should be a bottom-up initiative, not an objective in itself. Concerns have also been expressed about the impact of this strategy on smaller research groups that may find it difficult to join a network and, therefore, in lacking "EU accreditation", may find themselves excluded from other funding sources. Finally, although a simplification of the application procedure is envisaged, the EC proposal does not refer to the evaluation of the grant application. It is thus of paramount importance to stress that scientific excellence must remain the most important selection criterion. To restore trust amongst the scientists puzzled by the composition and obscure mode of action of the evaluation panels of previous FPs, an improved peer-review system for the selection process should be established. National agencies representative of the research community could, for instance, be entitled to carry out jointly the evaluation or to provide lists of expert assessors.

The EC proposal outlines seven priority areas of research. Four of these are relevant to the life sciences—genomics and biotechnology for health, food safety and health risks, sustainable development and global change,

and nanotechnologies, intelligent materials, and new production processes. The definition of the thematic priorities, however, is still vague and will have to be altered to prevent the exclusion of whole research areas of socio-economic and scientific importance. Food safety and health risks, for instance, cannot be restricted to technology development and should include plant and animal science. Redefinition is also crucial because national programmes, particularly in smaller EU member states, are strongly influenced by orientations of the framework programmes. Scientists should, therefore, be more directly involved in the identification of strategic areas likely to produce substantial breakthroughs.

The EU's researcher-mobility programmes have long been a success story, promoting development of expertise and transfer of knowledge. Novel measures, including specific actions for women, and the proposed increase in mobility grants, notably for researchers from countries not associated with the EU, should keep the new programme on the same track. Still missing are details concerning return and re-integration mechanisms. The scientific community is longing for a career-development scheme enabling talented young scientists to establish their own group by providing funds for consumables and personnel. Return and career development mechanisms are absolutely essential to reduce the brain drain not only to the USA but also within Europe, from south to north and, with the EU enlargement, from east to west, and to anticipate the forthcoming generation shift among senior investigators all over Europe. Also needed are political measures (eg, fiscal status) dismantling obstacles to researcher mobility, but these do not lie directly in the hands of the EC.

In conclusion, the EC has handed in homework that still requires clarification but is promising in that it considers some of the major concerns of the scientific community. That the EC and the European Council and Parliament seem to be willing to start a real dialogue with the various stakeholders of the sciences is also an appreciable move for the future. A revamped framework programme will not, however, remove the major problem of European research, which is the low level of funding. The planned FP6 budget, 17.5 billion euro, represents an increase of 17% on FP5. But the framework programme accounts for only a minor part of the total research funding in Europe (5.4% under FP5), which lags way behind that of Japan of the USA in terms of percentage of GDP.⁴ Reversing this trend is eventually where the real challenge of stimulating European research lies.

The European Life Sciences Forum (www.elsf.org) is a recent initiative that gathers together representatives from all disciplines of the life sciences to foster the dialogue between scientists, society, and policy-makers and, more specifically, to act as an interface between the scientific community and the European Institutions (ie, Commission, Council, and Parliament).

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