

EMERGENT HUMAN DISEASES: ALLERGIES - AUTISM - MYALGIC ENCEPHALOMYELITIS (ME)

MEETING OF THE PARLIAMENTARY AND SCIENTIFIC COMMITTEE ON TUESDAY 17TH JUNE 2008



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Allergies

There seems little doubt that allergies have increased in recent years. It seems that this is not merely greater awareness or previous misdiagnosis but a true increase in the prevalence of allergies, in particular anaphylactic reactions.

The Inquiry

The House of Lords Select Committee on Science and Technology was tasked to investigate this. In setting up the enquiry and looking at the three previous reports in the last five years, from the Royal College of Physicians, the House of Commons Health Committee and the Department of Health, it seemed that lack of provision of allergy services had been of major concern. But, it was clear from our enquiry that little had been achieved and the shortfalls in clinical services remained unaddressed.

As the inquiry developed, it became shockingly apparent just how severely allergic diseases could impair people's quality of life and how, despite our

track record of high quality research in the field, allergy services in the UK lag far behind those of other European countries through a severe shortage of allergy specialists.

During our inquiry we heard of children with allergies who sleep poorly by night and are bullied at school by day, and whose hay fever impairs their performance in summer exams. We learnt that the workplace environment can cause or so exacerbate allergic symptoms that some adults are forced to give up work, yet there is no clear guidance about what to do next or how to control their symptoms. And we heard of the increasing problem of fatal anaphylaxis, particularly through insect stings and food allergies.

Allergic mechanisms

Allergy underlies a wide spectrum of conditions. With anaphylaxis, most commonly caused by nuts or bee stings, there is a very rapid onset of swelling of the tongue and respiratory passages leading to collapse, and even to cardiac arrest and death. Less acute reactions result in a severe local

reaction to contact with various allergenic substances. Some reactions take a little longer for onset and include severe skin rashes. Other more chronic reactions include contact dermatitis, eczema and food allergy responses of the skin and the gut, and delayed hypersensitivity reactions to drugs. Unfortunately some people believe that they are allergic to various external agents but extensive investigations show that this is not the case; these are better described by the broad term 'idiopathic environmental intolerance'.

The allergic mechanism is principally mediated through IgE antibodies which cause the release of histamine leading to anaphylaxis. In the more chronic reactions immune cells (T cells) are activated by the allergen and cause the release of cytokines, chemokines and other inflammatory markers. Some tests marketed commercially depend on the detection of IgG antibodies, which simply show that the person has been exposed at some time to a substance, but do not indicate that they have a true allergic response, nor do they indicate that the substance is harming the person's

health. The broad range of presentations means that accurate diagnosis, which depends in large part on very careful history taking, is absolutely key to management in the long-term.

During our enquiry, we learnt of people who spend time and money on treatments for which there is no benefit and we also learnt of many people whose true allergy goes untreated or mismanaged because of the lack of accurate specialist diagnosis. Some of the rare allergies, such as allergies to anesthetic, sometimes require specialist investigation which is only undertaken in one or two centres in the UK.

The size of the problem

Our committee also found we could not quantify the problem, the full health cost of allergies or the economic burden to society because the reporting systems in the NHS do not code specifically for allergy per se. Yet data from 2004-05 suggests that 3 million people consult their GP, at a cost of around £211-311million per annum, generating about 72.6 million prescriptions at a cost of almost a billion pounds – or 11% of the annual drugs budget.

We also learnt that there are at least 70,000 acute hospital admissions for asthma and 3,000 for anaphylaxis each year, costing in the region of £56-83 million in secondary care alone. And there are hidden costs; some patients believe they are allergic to drugs such as penicillin and so are always prescribed more expensive alternatives, when in fact they do not have a true allergy and have never been properly tested for the allergy.

Services in Europe

The committee found that allergy services in the rest of Europe are much more developed than in the UK, despite our history of excellence in

basic cellular science around allergy. We therefore made our key recommendations around clustering allergy services together to create centres of excellence. We want those services that already are involved in treating allergy and have an interest in allergy to come together in a grouping, led by a full time allergist, to create a centre. Such a centre would be able to provide education to primary and secondary care in their region, lead on research and also provide a resource to patients. Skin testing and complex allergy testing could be undertaken to ensure accurate diagnosis and a management plan evolved with the patient that could be monitored back in primary care. Where allergy is severe or life threatening and where patients have complex allergic disease, they need to have access to a centre of excellence.

Recommendations

We also made recommendations around the need to look at the way that those handling food are trained, because of the danger of nut and other allergen contamination in food. The whole peanut allergy story is currently being researched and it is worth noting that in Israel and Africa where children are weaned on peanut based preparations, they seem to have a lower incidence of peanut allergy than in this country. Here, the Department of Health advises pregnant women and lactating women to avoid peanuts; this advice is subject to review although our committee felt the advice should be withdrawn pending the review.

Children with hayfever can drop up to a grade in major exams which occur during the hayfever season. However these children rarely get extra time in exams and sometimes are seated in an exam hall near a window, exposing them to higher levels of pollen than may be present in other parts of the exam hall. School teachers may not be adequately trained to deal with

anaphylaxis. If a child with a dangerous nut allergy has forgotten to bring their EpiPen to school, and is exposed to nuts, the school does not have a generic adrenalin single-dose pen available to give as emergency first aid. When anaphylaxis occurs time is of the essence.

In Europe immunotherapy is available and widely used for managing some allergic disease, but many of these immunotherapy products are not licensed in the UK and therefore have not been put before NICE for appraisal. Until they are licensed here, patients in Europe will have a range of treatments available to them that do not exist in this country.

Atmospheric pollution, particularly diesel exhaust particles contribute to allergy; those living close to areas of high diesel fumes seem at greater risk of developing allergies, as well as at risk of poor lung development as they grow up.

The future

Many theories have been advanced as to why allergies are on the increase, from the 'hygiene hypothesis' through a range of other proposed explanations. However none of them is clearly proven and it seems that the causes of allergy are probably multi-factorial. Without good ongoing epidemiological research, we will never unscramble who is most at risk let alone what can be done to change the trend of an increasing number of allergies manifest in our society.

The House of Lords report has been universally welcomed by patient groups and clinicians alike and has triggered the formation of co-ordinated working groups to try to improve allergy services across the UK. With the Government's backing, a small number of changes and a small amount of money could dramatically improve the service to patients.

Autism Spectrum Conditions

Simon Baron-Cohen

Autism is a *spectrum* condition, meaning that it is manifested to varying degrees of severity. At one extreme, a person may have no social

skills, no language, and major learning difficulties. At the other extreme, the individual may have average or even above average IQ, precocious

vocabulary (though a lack of interest in small-talk or chatting), and odd social skills (being one-sided or extremely self-centred). The former

would receive a diagnosis of *classic autism*. The latter would receive a diagnosis of *Asperger Syndrome (AS)*. Both of these are subgroups on the autistic spectrum. Both also share a strong preference for routines and repetition, and 'obsessional' interest in highly specific topics. Up to 1% of the population are somewhere on the autistic spectrum.

Psychological aspects

The *empathising-systemising (E-S)* theory proposes that there are empathising deficits in autism, whilst systemising is either intact or superior. *Empathy* involves imagining another person's thoughts and feelings, and having an appropriate emotional reaction to those feelings. Children and adults with AS show their empathising deficits on age-appropriate tests of emotion recognition, theory of mind, and spontaneous empathy.

Theory of mind (ToM) is the ability to attribute mental states to oneself or others and is regarded as the cognitive component of empathy. Emotion recognition is sometimes regarded as part of ToM because emotions are mental states. Often emotion-recognition deficits only appear if 'complex' emotions are tested, though in some individuals with autism the deficit is evident even when 'basic' emotions are tested. This deficit can make sense of the difficulties in social and communicative development, and in imagining others' minds.

Systemising is the drive to analyse a system in terms of underlying rules, in order to understand and predict its behaviour. People with autism spectrum conditions show precocious understanding of systems, relative to their mental age, on tests of intuitive physics or questionnaires assessing how interested a person is in different types of systems (maps, train timetables, machines, syntax, etc). The unusually strong repetitive behaviour, the strong desire for routines, and the 'need for sameness', can be seen as the result of a strong drive to systemise. Systemising also requires excellent attention to detail, and people with autism and AS are faster on visual search tasks. Strong systemising can therefore explain the strengths that people with autism and AS have.

Neurological aspects

Anatomical abnormalities have been identified in different brain regions in autism. These are not found in every case, and there are inconsistencies between studies, such that sometimes overgrowth is found, and sometimes undergrowth. The brain regions that have been reported to be atypical include the cerebellum, corpus callosum, hippocampus, and the amygdala.

Epilepsy also occurs in a proportion of individuals with autism spectrum conditions, though the exact rate is no longer clear. Although in classic autism it is well established that one third of cases develop epilepsy by adolescence, in the Asperger subgroup these rates may be much lower and have not been systematically studied. In terms of neuropathology, the number of Purkinje cells in the cerebellar cortex is abnormally low. Abnormalities have also been reported in the density of packing of neurons in the hippocampus, amygdala, and other parts of the limbic system. Abnormalities have also been found in the functioning of the amygdala, the orbito- and medial-frontal cortex. These atypical patterns of neural activity arise in relation to the empathising deficits.

Using MRI volumetric analysis, or measures of head circumference, some reports suggest the autistic brain involves transient postnatal macrocephaly. For example, neonates later diagnosed with autism have normal head circumference, but by 2-4 years of age 90% of these have MRI-based brain volumes larger than average. This may reflect an enlargement of cerebellar and cerebral white and grey matter.

Genetic aspects

The sibling risk-rate for autism shows a five- to ten-fold increase over general population rates. It used to be said that the sibling recurrence rate was much higher than this (50-100-fold), but this was based on old epidemiological prevalence rates of autism being 4 per 10,000, whereas today we recognise that 1% of children have an autism spectrum condition. The sibling recurrence rate is 5-10%.

Regarding twin studies, when a narrow phenotype (definition) is considered, 60% of monozygotic (MZ) pairs are concordant for autism versus no dizygotic (DZ) pairs. When a broader phenotype is considered, 92% of MZ pairs are concordant as compared to 10% of DZ pairs. Molecular linkage genetic studies have led to a number of chromosomal regions being implicated, such as 2q, 7q, and 15q. Loci on the X chromosome have also been implicated in autism, which may explain the sex ratio (markedly biased towards males), though these obviously cannot account for cases of male-to-male transmission.

Early diagnosis and intervention

The earliest that classic autism has been reliably diagnosed is 18 months of age. This has been shown using a screening instrument (the CHAT, or Checklist for Autism in Toddlers) which tests for the absence of 'joint attention' behaviours such as pointing and gaze following, and the absence of pretend play, all of which are normally present by this age. Population-based studies show that the CHAT has excellent specificity (children who fail on this test have a 83.3% chance of developing autism or a related pervasive developmental disorder), but low sensitivity (it only detects 2 out of every 5 cases, mostly missing the Asperger subgroup). Revisions of the CHAT are under way to improve the instrument further. Asperger Syndrome can be reliably diagnosed by age 5 years. This has been shown using a screening instrument called the CAST (Childhood Asperger Screening Test).

The most effective interventions for children on the autistic spectrum are special education, such as social skills teaching, and Applied Behavioural Analysis (ABA), where appropriate skills and behaviours are taught through principles of reinforcement. The key ingredients for effective early intervention are that the methods are highly structured, intensive, and individualised. Appropriate cognitive interventions are also beneficial for teenagers and adults.

Medical treatments are not usual. Indeed, there are ethical issues

surrounding the notion of trying to 'cure' autism. Although some aspects of the condition do require help (eg the empathy difficulties), other aspects may not (eg the systemising talents).

The cost of autism spectrum conditions

Knapp and Jarbrink in 2007 calculated that autism costs the UK £28 billion per annum, with the cost per individual with autism being £2.9 million over their life time. Such estimates include the impact on families that can be major.

Putting intervention on a rational basis

For many years, 'treatment' in autism has proceeded on the basis of an approach that has been tried and tested but without any real rationale for why it should be effective. Newer interventions, in contrast, are designed to harness individuals' areas of strength and their natural interests as a means for building new skills. Two examples of these are: (a) teaching emotion-recognition via computers using the *Mindreading* DVD educational software; and (b) teaching emotion-recognition by presenting emotional expressions on toy vehicles using the *Transporters* animation. In the case of the *Mindreading* DVD (www.jkp.com/mindreading), the individual's natural interest in lawful, predictable computers and in

information being systematically organised renders the domain of emotions easier to learn about. In the case of the *Transporters* animation (www.transporters.tv), the child's natural interest in the mechanical, predictable motion of vehicles means they are attending to the film, thereby enabling implicit learning of emotions since these are grafted onto the vehicles (See Figure). In this way, the domain of emotions is separated from their usual context (real-time social interaction). Rather than expecting the child with autism to join the social world, with all its attendant unpredictability, social information is taken to the child's safer world of computers or mechanical vehicles. Such methods of intervention are rational in that they are based on cognitive theory (in this case hyper-systemising).



Some useful links

The National Autistic Society is the main charity in the UK for families with a child on the autistic spectrum: www.nas.org

The Autism Research Centre, Cambridge University, contains a searchable database of publications and screening instruments: www.autismresearchcentre.com

As interventions are scientifically evaluated, the results of such studies are summarised at www.researchautism.net

Further Reading

Autism and Asperger Syndrome: The Facts (Simon Baron-Cohen, 2008, Oxford University Press.



Figure: Screen shots from *The Transporters* (www.transporters.tv)

M.E. (Myalgic Encephalomyelitis) – A Research orphan for too long!

Peter Spencer

Introduction

Almost everything about M.E. is contentious – even the name. It is a complex and invisible illness which stigmatises people and completely destroys the quality of their lives. We know little about the epidemiology, aetiology and pathogenesis. With an estimated 250,000 people in Britain directly affected – around one million including loved ones and carers – it affects much larger numbers than is

generally realised.

M.E. is believed to be the greatest single cause of long-term absence from school for children. Overall the social and economic costs of M.E. to the country have been estimated at £6.4 billion per annum. Successive reports over the past 20 years – including most recently the Gibson Inquiry – have strongly recommended that the Government funds much more research. This raises hopes that are not

then realised. Why is it so difficult to achieve what is obviously so necessary?

What M.E. does to people

M.E. has a devastating impact on people. Its symptoms include overwhelming exhaustion and malaise, cognitive difficulties and poor concentration ('brain fog'), joint pain, muscle pain, sleep disturbance, digestive problems, sensitivity to light

and a whole range of other painful and distressing problems.

The most severely affected become housebound and often bedbound for years. A recent survey by Action for M.E. showed that 77% of those who were in employment lose their jobs. A fortunate minority of those somehow struggle back to a level of health that enables them to work. A much more typical example however is Sue, a former university lecturer. Sue was a very active sportswoman and mountaineer before she was struck down by M.E. at the age of 26. She tried hard for years to resume her academic career. Eventually at the age of 42 she reluctantly accepted medical retirement. The life which was so full of promise has been taken away from her.

In addition to severe health and financial problems, patients encounter extraordinary levels of ignorance, scepticism and rejection. The stigma affects the behaviour of friends, close family and all too often health and social care professionals.

Epidemiology

Information on incidence and prevalence is still fragmentary and contradictory. But there is ample evidence that M.E. is not a new illness. Florence Nightingale and Charles Darwin both had symptoms which would probably give rise to a diagnosis of M.E. today. What we have here then is not so much an emergent disease as a disease about which there is at last emergent recognition and awareness.

So what can we say with any degree of confidence about M.E.? This is a really tough question because there is no explicit diagnostic test and no biological marker for the disease. Early studies into prevalence were extrapolations from studies which were recognised to be too small. Comparisons were hampered by different definitions. Nevertheless a number of studies seemed to point towards a population prevalence in the region of 0.4%. This has become the

provisional figure in the UK until better data are available. Several large scale studies in the USA indicate a figure of around 0.4%, except for one which claims a significantly higher rate but was based on a much broader definition that clearly includes other conditions in which chronic fatigue is a factor. We also know that this is not a disease confined to the developed world. Studies in Nigeria, India and Brazil suggest that M.E. is present in those countries with a prevalence up to around 0.6%.

Large scale international studies into the epidemiology are important because they will reveal vital clues that will help us to target research into disease mechanisms more intelligently. There is evidence of genetic predisposition and some variations in incidence related to ethnicity. We also know that a large proportion of cases are precipitated by a viral attack from infections such as glandular fever, viral meningitis, viral hepatitis etc. A general hypothesis held by many in the field is that in some people infection produces a persistent abnormality of the immune system and that immune mediators cause central and peripheral neural dysfunction. But not all viruses trigger M.E. and epidemiology studies which capture precipitating factors therefore open up ways of understanding how the immune system malfunctions in a person with M.E.

In addition to global studies, we also need to understand the national epidemiology of the illness. This will produce more reliable figures for incidence and will also identify specific environmental and other risk factors. One such study taking place through the M.E. Observatory is funded by the Big Lottery Fund. The research objectives are to pilot a national disease register for M.E. and conduct epidemiology studies in London, Hull and East Anglia.

The wider research agenda

The Chief Medical Officer published a report in 2002 which set out a

compelling case for making M.E. a high priority within the NHS and emphasised the urgency for research. The MRC responded by drafting a preliminary research strategy which emphasised the need for epidemiology to shape the research agenda, and issued a notice indicating special interest in this area and inviting research proposals. It also placed a priority on treatments and assessment of treatments rather than focusing on the disease mechanisms.

From 2004 the MRC co-funded with the NHS two large scale trials. PACE is assessing the merits of 'pacing' (energy management) and involves 600 people attending hospital outpatients across seven centres in the UK. FINE is a nurse-led rehabilitation programme for 360 patients in their own homes in the Manchester area. The MRC has since funded several much smaller studies into risk factors. However the expectations raised by announcements in 2003 have not been met and this has not been for lack of submissions. The question therefore is why this resulted in such a pedestrian and deeply disappointing outcome?

The MRC argues that competition for research funds is fierce and points out that the overall success rate of applications is only 20%. Assessment criteria are tough. Evaluating the merits of research proposals is challenging in an organisation which has not dealt with such complexity. Perhaps the weight given to the track record of research applicants handicaps newcomers into the field and tends to perpetuate research enquiry along the lines of earlier approaches. The position today is that there is widespread disappointment amongst patients about how little research into M.E. has been funded by the Government since 2003, especially the lack of research into the most severely affected, children and disease mechanisms.

A research summit workshop co-sponsored in November 2006 by the MRC and Action for M.E identified barriers to success including:

- No one discipline owns the illness and can treat it alone – it is an orphan and it is heterogeneous
- Insufficient inter-disciplinary collaboration in research
- Insufficient funding for pilot work
- Discouragement of potential researchers from becoming involved

Professor Stephen Holgate is considering the possibility of the MRC setting up a national research workshop to re-energise the whole UK national programme of research into M.E./Chronic Fatigue Syndrome.

The niche role of charities in research

Action for M.E. acts as a catalyst for research. Last year we received 21 research funding applications. We are about to announce our selections. The budget is modest at £80K but will enable the selected teams to develop their proposals into more robust propositions for mainstream funding by the MRC, NHS or other funders. We also aspire to attract high calibre researchers into the field by funding research fellowships and PhD Scholarships. Most importantly we shall continue to represent the patient voice at the heart of this crucial element of government decision making.

Conclusions

M.E. is a horrible illness which wrecks the lives of far too many people. Its stigma adds to the immense difficulties faced by patients. Many endure years of acute physical pain, financial deprivation and institutionalised injustice.

A major contributory factor is scientific ignorance. This must now be addressed as a national priority by deciding who in Government should lead and then holding them publicly accountable for delivering a re-invigorated and more robust research programme. This should be centred upon the best interests of patients and recognise the need to keep them routinely informed of progress.

During discussion the following points were raised:

The increased rates of autism could be attributed to growth of services and greater awareness, but this lacks scientific proof. It was suggested in the MMR debate that vaccines, or something in them, was toxic, although autism in Japan continued to rise even when MMR was withdrawn. In Denmark half the population who had received the vaccine showed no difference in rates of autism from the other half who had not. There is no scientific way of testing what the increase is due to. It is better therefore to point to mundane factors that every small town in Britain now has a child development centre capable of diagnosing autism, whereas 40 years ago you had to go to a specialist centre.

For allergies there is the hygiene hypothesis, where East German children had a much lower incidence of allergies living in a much more polluted environment before the wall came down. After re-unification the East German rates went up. Proximity to motorway junctions, exposure to diesel fumes and the packaging of food products may have also have some effect. There have been major changes in diet and children today may be junk food babies. For M.E. it is difficult to obtain a reliable diagnostic test for this disease although it may result from failure to recover from a viral attack. Further training of General Practitioners is required.

There is not such a vocal lobby group for vaccine damage in the UK as the cause of autism (which arose from the work of Dr Andrew Wakefield) as there is in the US. Environmental factors should not be ruled out and the genetic evidence does not indicate 100% heritability. Until evidence for an environmental factor is very strong we should be cautious about attributing blame, which is likely to be multi-factorial. The current rates of recorded autism may be much closer to the true rate due to better diagnosis, although this was disputed. The possible role in autism of mercury preservative in vaccines given to young children was dismissed.

There is a genetic component to allergies, but unpicking that from other factors may be very complex. You can't change your genes which have been fixed, although your genetic expression may be altered by environmental factors. Families with the eczema-asthma group of allergies exist, but may grow out of it. Research requires distinction to be made between the things that you can and cannot change. Autism is not 100% genetic as gene-environment interactions occur which can result in genetic predisposition being enhanced by unknown environmental factors which switch genes on and off.

The 'Not Invented Here Syndrome' may result in less attention being paid to scientific research done elsewhere. Access to population databases is important for multifactorial interpretation although access suffers from restrictions due to confidentiality issues that prevent their use in fundamental research into disease controlling factors. Community healthcare has been developed at the expense of the creation of centres of excellence with regulatory hurdles restricting scientific research.