107 A3243G index cases formed a representative sample. Despite studying a larger cohort of patients, we were not able to confirm the positive association between the A12308G polymorphism and an increased risk of stroke in patients with the A3243G mutation as reported previously.[2] Meta-analysis of all the available data failed to prove any clear association between the A12308G polymorphism and stroke-like episodes.

The clinical diversity associated with the A3243G mutation clearly involves multiple factors. We have previously shown a correlation between clinical phenotype and mutation load in muscle.[1] Age may well be a contributing factor, although there was a tendency for patients with stroke-like episodes in our group to be younger than those without. This argues against age as a risk factor for stroke-like episodes, as seen in common stroke.

Importantly our findings serve to highlight the difficulty of performing association studies on small numbers of patients. This is particularly difficult for mitochondrial genetic association studies because of the high variability of the mitochondrial genome. Understanding the phenotypic differences between patients with specific, pathogenic mtDNA mutations will ultimately involve studies of large cohorts of patients, unless we are able to gain clues from experimental studies that may highlight factors involved in the altered expression or segregation of mtDNA mutations.

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Early symptoms of brain tumours

Malignant cerebral glioma is the most common adult primary brain tumour but surprisingly few studies report how patients with early symptoms present in primary or secondary care. A retrospective audit in south east Scotland found considerable variation in the referral of patients with primary brain tumours: only one quarter of 439 patients were initially referred directly to specialist centres.[1] This must relate in part to the way in which symptoms develop and the difficulty of distinguishing them from more common but less sinister problems. For example, a large case record review of initial symptoms experienced by 653 glioma patients presenting to the National Hospital for Neurology and Neurosurgery, Queen Square, London, between 1955 and 1975 found a relatively low prevalence of neurological problems such as epilepsy (38%), headache (35%), mental change (17%), and hemiparesis (10%); by the time of diagnosis the prevalences were 54%, 71%, 52%, and 43%, respectively.[2] Few studies focus on the accounts of patients and relatives. One qualitative interview study of 28 Swedish patients suggested that relatives noticed general changes including cognitive and personality change and took the initiative in seeking help more often than the patients themselves.[3]

The recently published last diaries of the politician and historian the late Alan Clark provoked us to reconsider the significance of early symptoms from the perspective of patients and their close relatives.[4] Clark provides us with a moving account of the gradual onset of symptoms from a glioma—fatigue, problems with thinking and concentration, and intermittent headache over nine months. He also describes vividly the anxiety of knowing something was wrong but without any explanation, before his tumour was diagnosed.

During a study of quality of life already described,[5] we had opportunity to visit glioma patients at home after diagnosis, to listen to their accounts, and to question relatives separately. Here we report data on 92 patients (table 1), suggesting a differing development of symptoms and problems from that described in their medical records, and a distinctly similar picture, in some, to that described by Alan Clark. Interviews tended to elicit histories of more subtle problems such as fatigue and cognitive and personality change almost as often as the neurological problems typically associated with brain tumours. Of the 48 patients with headache only two had developed no other symptoms by the time of diagnosis.

Our sample is limited to patients who were well enough for radiotherapy and to receive home visits after diagnosis. It therefore excludes those most disabled and confused at diagnosis and treated with steroids alone. The data only cover problems that had developed before diagnosis. We did not have access to primary care records to explore how symptoms were presented to general practitioners, but 41% (38 of 92) were referred to a neurologist. Of the 64 patients whom we questioned on the topic, 19% (12) were critical of the initial management by their general practitioner and 28% of 88 relatives thought there had been significant delay by the health care system as a whole. This issue remained salient for many, even after the patient had died. Of 56 whom we saw as part of a study after bereavement, one third (17) spontaneously mentioned concerns they continued to have about delay in diagnosis and the effect this might have had on quality of life or survival. The problems they identified ranged across primary, secondary, and tertiary care and included their perception that referrals had not been made quickly enough or that waiting for appointments and imaging had been excessive.

The lack of data on the development of symptoms means that current national criteria for urgent referral rely on data from patients presenting to specialised centres rather than on the predictive power of symptoms in the population attending primary and secondary care. The data elicited here confirm the earlier suggestion by McKeran and Thomas that the significance of headache may lie in its association with altered patterns of behaviour and disability.[2] Although retrospective accounts cannot be used to define predictive factors for earlier diagnosis, they do suggest some implications for future research and practice. First, more detailed study of patients' and relatives'

Table 1 Symptoms at diagnosis of malignant cerebral glioma recorded in hospital records versus those elicited at home interviews

Symptom or problem	Recorded in the hospital records (n = 92)	Elicited from patients and relatives at home interviews (n = 92)
Weakness	55 (60)	51 (55)
Headache	49 (53)	48 (52)
Epilepsy	35 (38)	44 (48)
Sensory loss	32 (35)	37 (40)
Cognitive loss	30 (33)	42 (46)
Dysphasia	29 (32)	23 (25)
Personality change	14 (15)	28 (30)
Fatigue	13 (14)	44 (48)

Values are n (%).

experience might help further define the subacute presentation of cognitive and personality change and their relation to other complaints. Second, the predictive power of neurological symptoms presenting to general practitioners could be explored using existing large primary care research datasets. Third, relatives of patients referred urgently should be asked to attend with them to clarify aspects of the history that the patient may be unaware of. Beginning to discuss openly the difficulty of earlier diagnosis may help families come to terms with this lasting aspect of their concern. This might also help repair unnecessary rifts in relations with general practitioners, who are best placed to provide local support and palliative care these patients so often need.

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Five year follow up of a patient with spinal and bulbar muscular atrophy treated with leuprorelin

Spinal and bulbar muscular atrophy (SBMA; MIM 313200) is an X linked late onset motor neurone disease characterised by slowly progressive proximal and bulbar muscle weakness, muscle atrophy, postural hand tremor, gynecomastia, and endocrine disturbances that include signs of partial androgen resistance. SBMA is caused by the expansion of a trinucleotide CAG repeat in the first exon of the androgen receptor (AR) gene encoding a polyglutamine stretch.[1]

Recently, Katsuno *et al*[2] reported that leuprorelin, a lutenising hormone releasing hormone (LHRH) agonist that reduces the level of testosterone release from the testis, rescued motor dysfunction and nuclear accumulation of mutant ARs in a male transgenic mouse model of SBMA. This result indicates that ligand dependent nuclear translocation of mutant ARs containing expanded polyglutamine is the main source of the pathogenesis of SBMA, and that leuprorelin suppresses this translocation. We read this report with great interest, because we followed up a patient with SBMA, who has been administered leuprorelin for 5 years to treat his coexisting prostate cancer.

Case report

A 75 year old male noticed bilateral finger tremor at age 57. At age 63, he noticed weakness in his arms. He was admitted to our hospital in December 1991, when he was 64 years old. On initial examination, he had bilateral gynecomastia. Neurological examinations revealed facial weakness and lingual atrophy with fasciculations. Mild muscular atrophy was observed in the proximal parts of the upper extremities. Muscle strength was approximately in the range of 3/5 to 4/5 in the proximal parts, and 5/5 in the distal parts of the upper extremities. Fasciculations were observed in upper and lower extremities. Deep tendon reflexes were either lost or markedly diminished. Babinski signs were absent. Laboratory examinations revealed that the serum creatine kinase (CK) level increased to 803 IU/l (normal range 43–239 IU/l). LH (5.9 IU/L; normal range 1.8–5.2 IU/L) and follicle stimulating hormone (20.5 IU/L; normal range 2.9–8.2 IU/L) levels were elevated. After his informed consent was obtained, high molecular weight genomic DNA was extracted from peripheral leucocytes of the patient according to standard protocols. Genetic analysis of the AR gene was performed and the expansion of a CAG repeat (45 repeats) in exon 1 of the AR gene was identified, leading to a diagnosis of SBMA.

At age 67, he developed weakness in the legs, and noticed difficulty in climbing up stairs or standing up from a chair. Serum CK levels gradually increased to 1717 IU/l at age 70. In January 1998, when he was 71 years old, he was diagnosed as having prostate cancer, and was intramuscularly injected with 3.75 mg of leuprorelin every 28 days, because leuprorelin inhibits production of testosterone and dihydrotestosterone (DHT), which enhances the growth of prostate cancer cells. One month after the start of treatment, he noticed that his gait disturbance was rapidly exacerbated; however, the gait disturbance returned to the level before the start of treatment by April 1998. After the episode of transient exacerbation, his muscle weakness and atrophy exhibited no apparent deterioration to date. On the contrary, an improved muscle strength was recorded in the neck flexor, biceps brachii, and quadriceps femoris muscles. Furthermore, serum CK levels gradually decreased from 1717 IU/L to 834 IU/L after the leuprorelin treatment (see fig 1). Levels of LH (<0.6 IU/L) or testosterone (<0.1 IU/L; normal range 1.2–8.0 IU/L) were decreased by the leuprorelin injections.

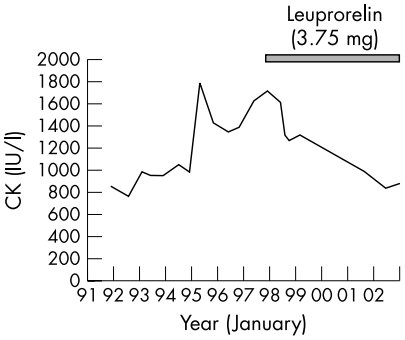

Figure 1 Serum creatine kinase (CK) levels of the patient gradually decreased from 1717 IU/L to 834 IU/L after the leuprorelin treatment.

Discussion

The experience of a 5 year follow up of this patient treated with leuprorelin is highly indicative of the following. Firstly, leuprorelin treatment induced a transient deterioration of the motor function in humans, as demonstrated in a transgenic mouse model of SBMA.[2] Secondly, after the initial transient deterioration, long term stabilisation of the motor function was obtained. Finally, leuprorelin treatment was effective even when the treatment was started in the advanced stage of the disease, although the patient's muscle weakness and atrophy have not completely disappeared. These findings provide grounds for the proposal made by Katsuno *et al*[2] that leuprorelin is a promising candidate for the treatment of SBMA.

At least nine neurodegenerative diseases are known to be caused by expanded CAG repeats. SBMA is unique among these diseases because the disease protein, AR, has a specific ligand, testosterone. It has been demonstrated that the nuclear translocation of ARs is solely dependent on testosterone. Recently, a transgenic mouse model carrying full length AR containing 97 glutamine repeats has been generated, and this model showed progressive muscular atrophy and weakness.[3] These phenotypes were markedly pronounced in male transgenic mice, which were significantly rescued by castration. Female transgenic mice exhibited only a few manifestations that markedly deteriorated with testosterone administration. Furthermore, in a *Drosophila* model of SBMA, it has been demonstrated that androgen agonists induce nuclear translocation of the mutant ARs and toxicity.[4] Taken together, this raises the possibility that blockade of nuclear translocation of the mutant ARs by hormonal intervention can provide therapeutic benefits in SBMA.

LHRH agonists including leuprorelin have been used for the treatment of prostate cancer. These drugs eventually inhibit LH production, which in turn inhibits production of testosterone and DHT, on which growth of prostate cancer cells depend. The alleviation or improvement of muscular weakness and decrease in the serum CK level in our patient may be due to the anti-androgen effects of leuprorelin. Interestingly, he noticed rapid exacerbation of gait disturbance one month after the administration of leuprorelin. It has been demonstrated that when LHRH agonists are administered continuously, the pituitary gland is initially stimulated, but after 5−12 days, the pituitary gland becomes