loquat leaves to lower triglyceride and increase HDL levels merits further investigation.

Authors’ affiliations
W R Saliba, L H Goldstein, M S Elias, Department of Medicine C, Hoa’mek Medical Centre, affiliated to the Technion-Israel Institute of Technology, Faculty of Medicine, Afula, 18101, Israel
G S Habib, Department of Medicine B, Lady Davis Medical Centre, affiliated to the Technion-Israel Institute of Technology, Faculty of Medicine, Haifa, Israel

Correspondence to: Dr W R Saliba; salibuss@yahoo.com
Accepted 6 December 2003

Tumour necrosis factor receptor associated periodic syndrome (TRAPS) with central nervous system involvement
K Minden, E Aganna, M F McDermott, A Zink

Tumour necrosis factor receptor associated periodic syndrome (TRAPS) is an autosomal dominant disorder resulting from mutations in the TNFRSF1A gene, characterised by recurrent attacks of fever, abdominal pain, severe myalgia, skin rashes, conjunctivitis, and/or periorbital oedema. These symptoms, which are partially explained by the unopposed action of tumour necrosis factor (TNF) owing to decreased soluble TNF receptor 1 (sTNFRSF1A) serum levels, can be alleviated by administration of etanercept, which is a TNFRSF1B (TNFRII) p75:Fc fusion protein.

We describe a family in which one of three affected members with central nervous system (CNS) symptoms developed a demyelinating disorder suspected to be a feature of TRAPS.

CASE REPORT
A 20 year old white man and his 25 year old sister had complained about recurrent attacks of fever, abdominal and loin pain, severe myalgia, skin lesions, sore throat, conjunctivitis, and periorbital oedema since early childhood. These attacks had come at irregular intervals, lasted for 2–3 weeks, and were accompanied by greatly increased acute phase reactants. During childhood both patients had received long term steroid treatment, which partially alleviated the symptoms; in addition, they had been treated with multiple immunosuppressive drugs (for example, chlorambucil, azathioprine, methotrexate) without any detectable benefit, under the erroneous impression they had Still’s disease.

The young man developed depressive symptoms without other signs of a neurological disease in his teens, while his sister experienced a neurological illness with dizziness and paraesthesia in her hands, feet, and around the umbilical area at the age of 22. At that time, conventional T2 weighted magnetic resonance imaging (MRI) of the brain disclosed multiple small hyperintense lesions (most were <6 mm), located in the supratentorial white matter, and some of which showed gadolinium enhancement on T1 weighted, spin echo sequences. The location of these lesions was not typical of multiple sclerosis; cerebrospinal fluid analysis showed pleocytosis and oligoclonal bands, while electroencephalography, visual and somatosensory evoked potentials, selective digital subtraction angiography, and a neurological examination were all normal.

The father of both siblings had also had periodic fevers in childhood, progressing in adulthood to intense localised muscle pain and profound stiffness, associated with depressive symptoms, memory impairment, and recurrent loss of sensation and power in his fingertips and hands. Both the clinical examination by a neurologist and the electromyography/neurography pointed to a myotonic disorder.

All three affected family members have a T50K mutation in exon 3 of the TNFRSF1A gene with associated low sTNFRSF1A levels; defective shedding of TNFRSF1A was demonstrated in the young man’s peripheral blood mononuclear cells on FACS analysis. Given the severity of attacks in both siblings, treatment with etanercept was started, which dramatically improved both patients’ wellbeing, with normalisation of laboratory values. An improvement in paraesthesia without further changes of the MRI findings occurred in the woman during the initial months of anti-TNF treatment. However, at month 20 of etanercept treatment unilateral optic neuritis developed and, compared with imaging performed 12 months previously, new demyelinating lesions were detected by fluid attenuated inversion recovery (FLAIR) MRI (fig 1). This clinical exacerbation occurred in what appeared to be the setting of a TRAPS flare, because fever, arthralgia, muscle stiffness, skin and eye lesions occurred concomitantly.

DISCUSSION
As increased TNF/TNFR signalling has a key role in TRAPS, and is also implicated in inflammatory demyelinating disease of the CNS, one may speculate that the CNS symptoms seen in the young woman are part of the TRAPS phenotype. This is supported by other reports of CNS symptoms in TRAPS, including a severe neurological illness in a woman with a T50M mutation, optic neuritis/papillitis in a woman with a C30R mutation, and behavioural changes in a man and his daughter with the R92Q variant. Whether the CNS symptoms in the woman’s brother and father, however, were also...
due to white matter disease is unknown, because imaging of the brain was not carried out in either of them and the presence of white matter disease was not proved conclusively by other examinations.

Etanercept has been shown to alleviate symptoms in about two thirds of patients with TRAPS, but it did not impede progression of the demyelinating disorder in this young woman. It remains unclear whether exacerbation of her neurological symptoms was an integral part of the disease flare or due to TNF antagonist treatment, as occasionally seen in patients with multiple sclerosis. Notably, another patient with TRAPS (T50M mutation) has also experienced paraesthesias and altered cognition while receiving etanercept (Hull K, personal communication).

Further research is necessary to verify whether CNS symptoms are part of the TRAPS phenotype or whether patients with TRAPS carry a particular risk of developing neurological complications owing to TNF antagonism. Meanwhile, clinicians should be aware of possible CNS involvement in TRAPS, with close monitoring of those patients receiving etanercept.

Accepted 19 November 2003

REFERENCES

Figure 1 MRI scans of the brain of the young woman taken at the time of worsening disease 20 months after starting etanercept. Axial FLAIR images demonstrate multiple small hyperintense lesions in the supratentorial white matter. However, none of the lesions were enhanced after intravenous injection of gadolinium on conventional T1 weighted, spin echo imaging.