The authors have no competing interests.

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Therapeutic interleukin (IL) 1 blockade normalises increased IL1β and decreased tumour necrosis factor α and IL10 production in blood mononuclear cells of a patient with CINCA syndrome

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Mutations in the cold-induced autoinflammatory syndrome 1 (CIAS1) gene cause inherited chronic autoinflammatory disorders such as Muckle-Wells/familial cold urticaria and chronic infantile neurological cutaneous and articular (CINCA) syndrome.[1 2] Up regulation of interleukin (IL) 1β was recently reported in unstimulated monocytes obtained from a patient with CINCA syndrome,[3] and active inflammatory disease resolved rapidly and completely during treatment with anakinra in patients with CINCA[4] and with Muckle-Wells syndrome.[5 6]

We report on a 47 year old male patient with the CIAS1 mutation T348M presenting classical clinical features of CINCA syndrome. The disease was refractory to conventional anti-inflammatory drugs and infliximab, but was successfully treated with daily subcutaneous injections of 100 mg of recombinant human IL1 receptor antagonist (anakinra, Kineret; Amgen, Cambridge, UK). Before and after therapeutic IL1 blockade, we assessed clinical and humoral inflammatory disease activity and cytokine release (IL1β, tumour necrosis factor α (TNFα), IL6, and IL10 in cell culture supernatants; R&D enzyme linked immunosorbent assay (ELISA) kits with lower detection limits of 3.9, 15.6, 3.13, and 7.8 pg/ml) from Ficoll-isolated and either unstimulated or lipopolysaccharide (LPS; 100 ng/ml) stimulated peripheral blood mononuclear cells (PBMC; 1×10^6/ml RPMI 1640 +5% fetal calf serum) after 48 hours of cell culture.

Cell-specific staining for monocytes was performed with mouse FITC-antihuman CD14 (eBioscience; San Diego, CA). Flow cytometry data were acquired only with propidium iodide negative cells on a FACSCalibur equipped with four lasers, and data were analysed using CellQuest software (BD Biosciences).

Concomitant symptomatic drug treatment was kept unchanged. Before anakinra treatment the patient showed typical clinical and serological signs of active inflammatory disease, including rash, polyarthritis of wrists and metacarpal joints, leucocytosis with neutrophilia, and a moderate acute phase response. After 2 days the rash completely vanished and synovitis and morning stiffness had markedly improved. After 3 weeks complete clinical remission with absence of cutaneous and articular symptoms was achieved. Raised C reactive protein levels and erythrocyte sedimentation rate normalised and leucocyte and platelet counts decreased, whereas monocyte numbers did not change and lymphocyte counts increased (table 1).

At the functional level we did observe an enormous IL1β release from monocytes after LPS stimulation before treatment. This dramatically and progressively declined upon treatment with anakinra. Surprisingly, the secretion of IL6 from activated PBMC was completely blocked, and similar to our previous finding in the same patient,[7] we observed a completely deficient IL10 and in this case a deficient TNFα response of monocytes to LPS stimulation before treatment. Therapeutic IL1 blockade, however, restored both, spontaneous as well as LPS-induced TNFα and IL10 secretion.

Based on the pretreatment findings on stimulation of PBMC in this patient, and in addition to our previous

Table 1 Laboratory measures in a patient with CINCA syndrome before and during treatment with recombinant human IL1 receptor antagonist

Measure	Baseline	3 Weeks	9 Weeks
C reactive protein (mg/l)	47	9	4
Erythrocyte sedimentation rate (mm/1st h)	40	3	8
Haemoglobin (g/l)	10.9	12.5	11.6
Leucocyte count (10^9/l)	15.6	8.1	9.4
Monocyte count (10^9/l)	0.47	0.50	0.47
Lymphocyte count (10^9/l)	1.4	2.87	2.87
Platelet count (10^9/l)	528	403	419
CD14+ cells among PBMC (%)	1.28	1.35	1.15
Cytokine secretion by PBMC (pg/ml)			
Spontaneous IL1β	<3.9	<3.9	<3.9
LPS-induced IL1β	8534	2943	271
Spontaneous IL6	<3.13	<3.13	<3.13
LPS-induced IL6	1921	<3.13	<3.13
Spontaneous TNFα	<15.6	225	188
LPS-induced TNFα	<15.6	732	220
Spontaneous IL10	<7.8	162	170
LPS-induced IL10	<7.8	163	175

finding,[7] we suggest that there is a defect of LPS responsiveness of monocytes to the induction of TNFα and IL10.

This case confirms the excellent response of CINCA syndrome to treatment with human IL1 receptor antagonist. Our results suggest that patients with this hereditary autoinflammatory disorder may exhibit a profound dysregulation of IL1 and TNFα synthesis. However, we cannot exclude the possibility that the inability to detect TNFα before application of IL1 receptor antagonist owed more to a rapid decay of TNFα rather than reduced production. As this dysregulation is reversed by treatment with IL1 receptor antagonist, one may argue that therapeutic inhibition of otherwise aberrant IL1β secretion results in a compensatory up regulation or less decay of TNFα to maintain the host's capacity to react to microbial agents and other types of danger signals. Furthermore, the overall up regulation of the TNFα pathway by interaction at the IL1 pathway illustrates that the cytokine imbalance is not due to a defect, but rather to a dysregulation. Finally, our results provide an explanation for the reason why TNF blocking agents are ineffective in certain autoinflammatory diseases.

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Reversible posterior leucoencephalopathy in scleroderma

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A 34 year old Chinese woman with limited scleroderma presented with rapid onset of mental confusion and generalised tonic-clonic seizures. Her blood pressure control had been unsatisfactory in the preceding 4 weeks despite the use of three anti-hypertensive agents, which included an angiotensin converting enzyme inhibitor. Malignant hypertension (blood pressure 240/140 mm Hg on admission) was evident, with typical fundoscopic abnormalities, microangiopathic haemolytic anaemia, and rapidly deteriorating renal function with acute oligouric renal failure (increase in serum creatinine from baseline of 86 to 495 μmol/l in 3 days). There was, however, no evidence of left ventricular failure.

Treatment was given in the intensive care unit with infusions of labetalol (up to 150 mg/h) and iloprost (up to 10 μg/h), large doses of captopril (150 mg/day), and haemodialysis. An urgent magnetic resonance imaging (MRI) scan

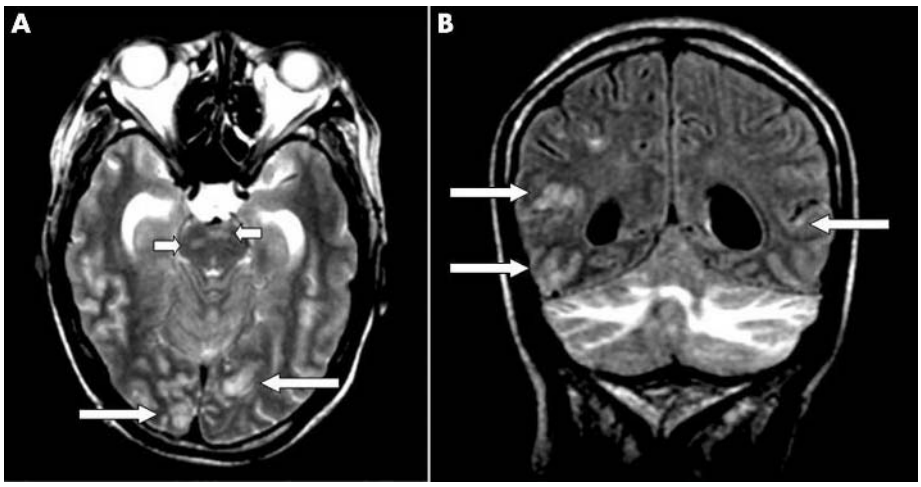

Figure 1 (A) Axial T_2 weighted and (B) coronal fluid attenuated inversion recovery (FLAIR) images showing bilateral abnormal hyperintensities in the white matter of the cerebellum, cortex, and subcortical white matter of the occipital lobes (long arrows), and in the brain stem (short arrows).