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Action myoclonus–renal failure syndrome: characterization of a unique cerebro-renal disorder

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Summary

Action myoclonus–renal failure syndrome (AMRF) is a distinctive form of progressive myoclonus epilepsy associated with renal dysfunction. The syndrome was not recognized prior to the advent of dialysis and renal transplantation because of its rapidly fatal course if renal failure is untreated. The first and only description of AMRF was in four French Canadian patients in three families (Andermann *et al*., 1986). We now describe 15 individuals with AMRF from five countries, including a follow-up of the four French Canadian patients, allowing a more complete characterization of this disease. Our 15 patients with AMRF belong to nine different families. Segregation analyses were compatible with autosomal recessive inheritance. In addition, our findings show that AMRF can present with either renal or neurological features. Tremor (onset 17–26 years, mean 19.8 years, median 19 years) and progressively disabling action myoclonus (onset 14–29 years, mean 21.7 years, median 21 years), with infrequent generalized seizures (onset 20–28 years, mean 22.7 years, median 22 years) and cerebellar features are characteristic. Proteinuria, detected between ages 9 and 30 years in all cases, progressed to renal failure in 12 out of 15 patients within 0–8 years after proteinuria detection. Brain autopsy in two patients revealed extraneuronal pigment accumulation. Renal biopsies showed collapsing glomerulopathy, a severe variant of focal glomerulosclerosis. This study extends the AMRF phenotype, and demonstrates a more extensive ethnic and geographic distribution of a syndrome originally believed to be confined to individuals of French Canadian ancestry. The independent progression of neurological and renal disorders in AMRF suggests a unitary molecular lesion

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with pleiotropic effects. Our results demonstrate that the renal lesion in AMRF is a recessive form of collapsing glomerulopathy. Genes identified for focal segmental glomerulosclerosis and involved with the function of the glomerular basement membrane and related proteins are thus good candidates. Treatment can improve quality of life and extend the lifespan of these patients. Dialysis and renal transplantation are effective for the renal but not the neurological features, which continue to progress even in the presence of normalized renal function; the latter can be managed with anti-myoclonic and anti-epileptic drugs.

Keywords: action myoclonus; renal failure; progressive myoclonus epilepsy; cerebro-renal disorder; autosomal recessive inheritance

Abbreviations: AMRF = action myoclonus–renal failure syndrome.

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Introduction

The progressive myoclonus epilepsies are a clinically and aetiologically heterogeneous group of disorders. They are characterized by the association of action myoclonus, generalized tonic–clonic epileptic seizures, and progressive neurological deterioration with ataxia and often dementia (Berkovic *et al*., 1986, 1993; Marseille Consensus Group, 1990).

Action myoclonus–renal failure syndrome (AMRF, OMIM 254900) is a rare form of progressive myoclonus epilepsy associated with severe renal dysfunction. The syndrome was not recognized prior to the advent of dialysis and renal transplantation because of its rapidly fatal course if renal failure is untreated. The first description of AMRF (Andermann *et al*., 1986) was in four French Canadian patients from three sibships who presented with tremor of the fingers and hands and proteinuria at 17–18 years of age. Severe progressive action myoclonus, dysarthria, ataxia, infrequent generalized seizures and renal failure ensued between 19 and 23 years of age. Intelligence remained normal in all four patients (Andermann *et al*., 1986). We had previously noted that a case published as 'pigment variant of neuronal ceroid lipofuscinosis' (Horoupian and Ross, 1977) had clinical and pathological features of AMRF. We are unaware of any other reports of this disorder (Andermann *et al*., 1986; Berkovic *et al*., 1986, 1993).

We now describe 15 individuals with AMRF from five countries, including a follow-up of the four French Canadian patients, allowing a more complete characterization of the clinico-pathological phenotype, genetics and natural history of this peculiar cerebro-renal disorder.

Methods

Patients

We studied the clinical features of 15 patients from nine families of different ethnic origin (Table 1, Fig. 1). Eleven new patients with AMRF were ascertained for the study. The patients were recruited from the Montreal Neurological Hospital and Institute, Hôpital Sainte-Justine and the University of British Columbia Hospital, Canada; Mayo Clinic, Scottsdale, USA; Royal Melbourne Hospital, Australia; Max-Planck-Institut für Psychiatrie, Germany; and the Neurological Institute of Havana, Cuba. Additionally, a detailed follow-up was conducted on the four original French Canadian patients described in 1986. Informed consent was obtained from all families, in accordance with all local institutional review board guidelines.

Genetics

A detailed genealogical history was obtained from each family. Family pedigrees, starting from the oldest generation provided and including extended family members, were constructed with the program Progeny 5.1.01 (Progeny Software). Family genealogy books provided by two French Canadian index patients helped establish a genealogical link between the two families.

Segregation analyses were carried out assuming complete, single and multiple incomplete ascertainment. The *a priori* method assuming complete truncate ascertainment was also employed (Stern, 1960; Thompson and Thompson, 1966; Andermann *et al*., 1976).

Data analysis

Relationships between variables were assessed via Pearson correlation, performed using SPSS version 11.0.1 for Macintosh (SPSS Inc.).

Results

The clinical features are summarized in Table 1.

Neurological features

Bilateral fine tremor of fingers and hands was the first neurological symptom with age of onset from 17 to 26 years (mean 19.8 years; median 19 years). Present at rest, the tremor was considerably increased by fine motor activities such as writing. Progression of the disease brought about progressive worsening of the tremor with involvement of head, trunk and sometimes the tongue. In the late stages of the disease, the tremor was largely replaced by severe multifocal action myoclonus.

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Table 1 *Clinical features of the patients*

ID	Gender	Ethnicity	Age at onset of symptoms (years)					Renal transplant (age in years)	Deceased			EEG	Neuroimaging	Mental status
			Tremor	Myoclonus	Seizures	Proteinuria	Renal failure		Age (years)	Cause	Autopsy			
P01	F	American	22	23	None	22	30	31	Living (35)	None	None	Normal bg with diffuse intermittent theta; multifocal spikes at times followed by slow waves associated with severe paroxysms of myoclonus	MRI: generalized atrophy (cerebral, cerebellar, upper cervical)	Normal
P02	F	Australian	21	29	26	9	9	13, 17, 18	32	Adult respiratory distress syndrome	Yes	Diffuse generalized slowing and muscle artefact secondary to myoclonus	MRI: mild generalized atrophy (cerebral, cerebellar, upper cervical)	Normal (depression)
P03	M	Canadian	22	25	28	22	23	24	34	Aspiration pneumonia	Yes	Inconstant photomyoclonic response	CT, normal; MRI, no structural abnormality	Normal (depression)
*P04	F	French Canadian	18	19	21	21	22	None	25	Renal failure	No	Slow bg at 6.5–7.5 Hz; irregular generalized s-w discharges increased by HV and IPS, at times confined to the central vertex or both occipital regions	CT: diffuse cerebral atrophy	Normal
*P05	M	French Canadian	18	21	22	18	20	21	34	n/a	No	n/a	n/a	Normal
*P06	F	French Canadian	18	23	23	18	23	24	29	Rejection of renal transplant	No	Diffuse slowing of bg; generalized photosensitive epileptogenic abnormality	CT: diffuse cerebral and cerebellar atrophy	Normal
*P07	M	French Canadian	17	21	21	17	22	22	25	Rejection of renal transplant	Yes	Generalized epileptic activity increased by HV	CT: diffuse cerebral atrophy	Normal
P08	F	French Canadian	25	25	25	30	none	none	35	n/a	No	Mild diffuse disturbance of bg; non-epileptic disturbance of cerebral activity over right central and left centro-temporal regions; recurrent synchronous epileptic bursts over both hemispheres during IPS	MRI: possible asymmetry of the amygdalae with increased signal on the left	Normal
P09	M	French Canadian	18	20	None	25	26	None	26	Renal failure	No	Normal sleep EEG	Normal	Normal
P10	M	French Canadian	19	19	None	23	None	None	Living (34)	None	No	n/a	n/a	Normal
P11	M	Cuban	17	20	23	15	21	Yes	n/a	n/a	No	n/a	n/a	Normal
P12	F	Cuban	19	21	21	18	23	Yes	n/a	n/a	No	n/a	n/a	Normal

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Table 1 *Continued*

ID	Gender	Ethnicity	Age at onset of symptoms (years)					Renal transplant (age in years)	Deceased			EEG	Neuroimaging	Mental status
			Tremor	Myoclonus	Seizures	Proteinuria	Renal failure		Age (years)	Cause	Autopsy			
P13	M	German	18	14	20	14	18	None	31	Aspiration pneumonia	No	Generalized spikes and s-w complexes	CT: mild generalized cortical atrophy; intracerebral right hemispheric parietal calcification; non-specific bilateral hyperintense lesions (5 mm below surface)	Normal
P14	F	German	19	20	20	30	None	None	Living (33)	None	No	Generalized slowing and spike and s-w complexes	MRI: diffuse atrophy	Slight cognitive impairment
P15	M	German	26	26	None	19	26	29	Living (32)	None	No	Spikes, polyspikes, s-w complexes increased during IPS	MRI: diffuse atrophy and unspecified white matter lesion	Slight cognitive impairment

P = patient number according to pedigrees (Fig. 1); *original French Canadian patients (Andermann *et al*., 1986); none = not applicable to patient; n/a = information not available; bg = background; s-w = spike–wave; HV = hyperventilation; IPS = intermittent photic stimulation.

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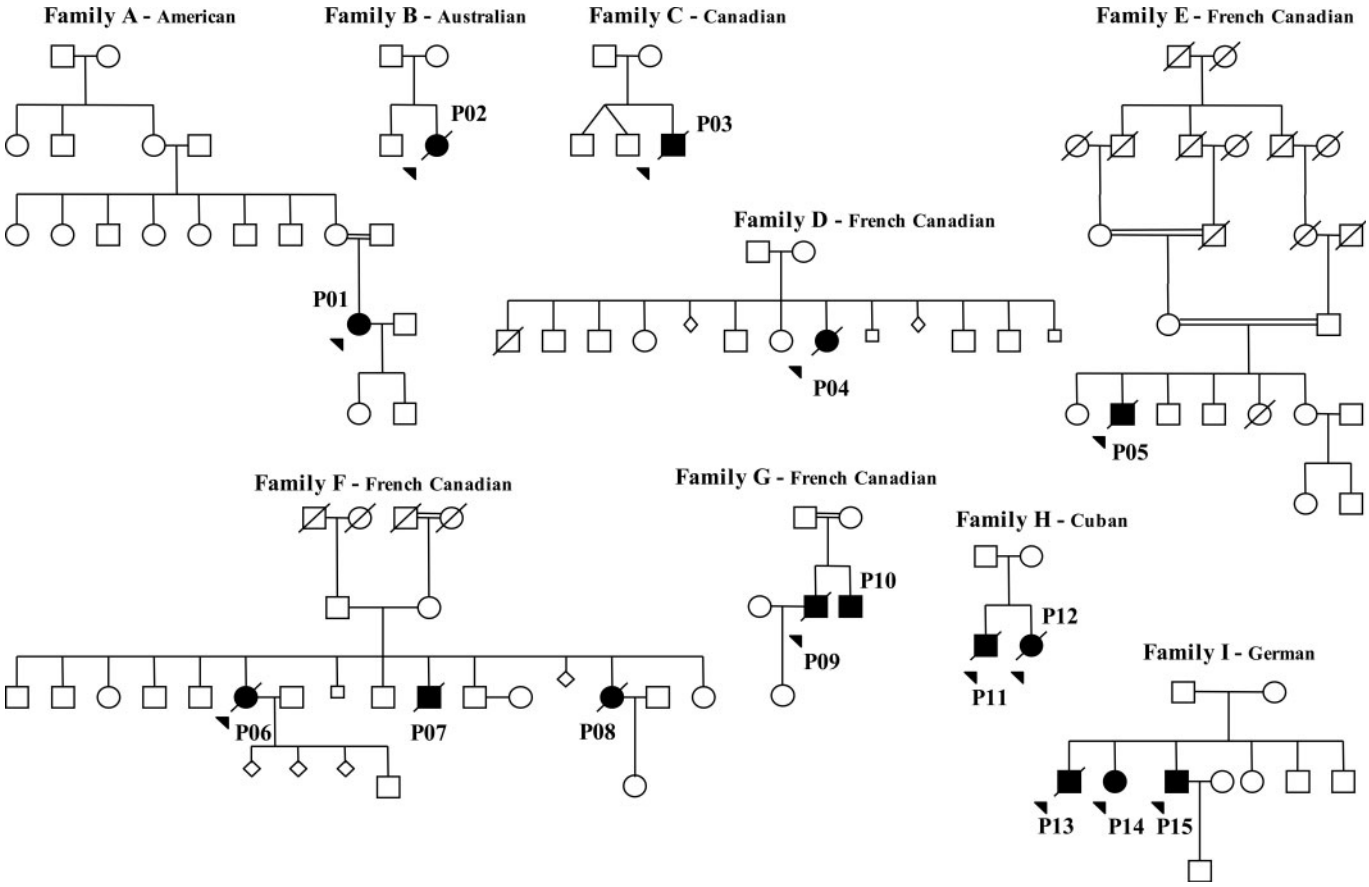

Fig. 1 Pedigrees. □ = male; ○ = female; ▨ = deceased male; ∅ = deceased female; ◇ = miscarriage; □ = male stillbirth; == = consanguineous marriage; △△ = dizygotic twins; ◥ = proband; ■ = male with AMRF; ● = female with AMRF.

Onset of action myoclonus was from 14 to 29 years (mean 21.7 years; median 21 years). Conversation, concentration, anxiety and fatigue worsened the myoclonus. Speech, attempted and executed, induced bulbar myoclonus. Palatal myoclonus was not present. The myoclonus was reflex-sensitive to touch on distal extremities. Some patients exhibited occasional jerks in response to startle. Asynchronous jerks of variable severity of the arms and/or legs, facial and truncal myoclonus were also present at rest. Action myoclonus proved to be the most debilitating feature of the disease; treatment with multiple anti-epileptic and anti-myoclonic drugs including valproate, clonazepam, barbiturates and piracetam was partially effective. In the final stages, myoclonus rendered the patients bedridden or wheelchair-bound with lap, trunk and leg belts.

Convulsive seizures occurred in 11 out of 15 patients (73%); onset ranged from 20 to 28 years (mean 22.7 years, median 22 years). Diurnal or nocturnal in nature, the seizures started with a generalized clonic phase with preserved consciousness proceeding to unconsciousness with tonic–clonic features. Frequency of the seizures ranged from one to nine per annum initially. Control of major seizures was achieved with anti-epileptic drugs, despite ongoing active myoclonic jerks.

Ataxia and dysarthria were observed in all patients as the disease progressed. Although it is difficult to distinguish ataxia from action myoclonus, neurological evidence of cerebellar abnormalities, namely pendular reflexes, abnormal rebound, and nystagmus found in some patients, was further indicative of an underlying ataxic component.

Thirteen patients were of normal intelligence, and two were regarded as having slight cognitive impairment. It was striking that there was no evidence of the intellectual deterioration and dementia characteristic of that seen in most other forms of progressive myoclonus epilepsies such as Lafora disease and the adolescent and adult forms of neuronal ceroid lipofuscinosis (Kufs' disease). Two patients had significant depression.

No patient had clinical evidence of a peripheral neuropathy. The results of peripheral electrophysiology were available on six patients in four families, and only one of three affected siblings in a German family had evidence of a predominantly axonal neuropathy. The results in the other two siblings showed some abnormalities, but were difficult to interpret. Three other unrelated patients had normal findings.

The main EEG findings were generalized epileptiform abnormalities, often photosensitive, as well as diffuse slow wave disturbance of background activity. Background activity was normal in some patients. At times, single spike and

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slow wave discharges were recorded corresponding to the myoclonic jerks.

Neuroimaging with CT or MRI was obtained in 11 patients and was reported as normal in three, whereas eight had diffuse cerebral atrophy often associated with cerebellar atrophy.

Renal features

Proteinuria occurred in all cases and was detected between ages 9 and 30 years (mean 20.1 years, median 19 years). In some patients, proteinuria was detected during routine testing for pregnancy, minor surgery or military medical exam. Progression of renal impairment to renal failure requiring dialysis and/or transplantation occurred in 12 out of 15 patients within 0–8 years (mean 3.8 years, median 4.5 years) after proteinuria was recognized. Nine out of 15 patients had had a renal transplantation by the time of their last follow-up. These were performed between the ages of 13 and 31 years in seven patients where the information is known (Table 1). One patient (P08) died of complications of neurological involvement 10 years after neurological onset and 5 years after proteinuria was detected without significant further renal impairment; two living patients (P10 and P14) have not yet proceeded to renal failure, with follow-up of 15 and 14 years, respectively.

Relationship between neurological and renal features

In five patients, the first symptom was neurological (tremor and/or myoclonus), whereas in four, renal dysfunction was detected before the onset of tremor or myoclonus. In the remaining six patients, neurological and renal features were detected more or less simultaneously. There was no correlation between the ages of onset of proteinuria and tremor (Pearson $R = 0.28$; $P = 0.31$), nor between renal failure and myoclonus onset (Pearson $R = -0.168$; $P = 0.60$). Nine patients died at ages 25–35 years (mean 30.1, median 31 years), 7–23 (mean 12.4 years, median 11 years) years after onset of the first symptom. In three, death was related primarily to respiratory complications of the neurological syndrome; in four, it was due to renal failure or complications due to renal transplantation or dialysis.

Genetics

The 15 AMRF patients belonged to nine different families and originated from Canada, Germany, Cuba, Australia and the USA (Fig. 1, Table 1). Four families (families D, E, F and G) were of French Canadian descent and originated from rural areas of southern Québec. A common ancestral surname linked two families to immigrants from Ile de France and Normandie, adjacent provinces in 17th century France, suggesting a founder effect. The fifth Canadian family (family C, P03) was not French Canadian, but had possible French ancestors on both sides, and the family from the USA (family A, P01) had one ancestor with French origins. There were no known French Canadian or French ancestors in the other three families.

We determined that the mode of inheritance in these families was autosomal recessive, based on the absence of affected cases in previous generations, two or more affected siblings in four families, verified parental consanguinity in three families, and parental origins from the same rural areas in six families (families F and D). Table 2A shows the distribution of affected individuals in the nine sibships. Segregation analyses assuming complete, single and multiple incomplete ascertainment were compatible with autosomal recessive inheritance (Table 2B). The *a priori* method (Table 2C), comparing the number of affected observed and expected assuming complete truncate ascertainment, was also compatible with autosomal recessive inheritance [$\chi^2(4) = 1.671$, $P > 0.80$].

Pathology

Neuropathology

Post-mortem examination of the Australian patient (P02) was available and was compared with that of the previously published Canadian patient (P06) (Andermann *et al*., 1986). The fixed brain of the Australian case weighed 1380 g. External examination was essentially normal and no abnormality was identified in serial coronal slices of the cerebral hemispheres and brainstem and sagittal slices of the cerebellum.

Histological examination showed accumulation of irregularly shaped, refractile and autofluorescent granules of pigment, up to 10 μm in their greatest dimension. These were most prominent in laminae I and II of the cerebral cortex, in the globus pallidus and putamen, and in the layer of Bergmann astrocytes in the cerebellar cortex. The granules appeared both separate from and adjacent to glial cell nuclei, suggesting that at least some were within astrocytes. Pigment granules were not seen in the thalamus, brainstem nuclei, dentate nuclei of the cerebellum or spinal cord grey matter. The pigment granules showed golden brown autofluorescence in unstained deparaffinized sections (Fig. 2A and B), stained black with Sudan black (Fig. 2C), dark blue–black with Luxol fast blue (Fig. 2D), golden brown with haematoxylin and eosin (Fig 2E and F), orange–brown with periodic acid–Schiff (PAS; Fig. 2G), and were negative for Perls' iron stain. Neurons in the cerebral cortex showed an accumulation of pigment consistent with lipofuscin that did not appear excessive. No significant loss of cerebral cortical neurons or Purkinje cells was seen.

Electron microscopy, undertaken on cerebellar cortex, in the layer of Bergmann astrocytes, showed electron-dense deposits which appeared to be formed by concretion of globules ~0.6 μm in diameter (Fig. 2H). A membrane was noted to surround the deposits incompletely, suggesting an intracellular location. Many of these deposits had both dense and paler areas. Within the denser areas, lamellae were often

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Table 2

A Distribution of affected individuals in nine Sibships

Sibship size*	No. of affected individuals per sibship			Total	%
	1	2	3		
1	1	0	0	1	11.11
2	1	2	0	3	33.33
3	1	0	0	1	11.11
6	1	0	1	2	22.22
9	1	0	0	1	11.11
11	0	0	1	1	11.11
Total	5	2	2	9	
%	55.6	22.2	22.2		100

B Sibling analysis assuming various methods of ascertainment

Methods of ascertainment	Affected	Unaffected*	Total	% Affected
Raw data	15	27	42	35.7
Complete	16	49	65	24.6
Single	6	27	33	18.2
Multiple incomplete	11	33	44	25.0

C Application of the *a priori* method for an autosomal recessive mode of inheritance assuming complete truncate ascertainment

Sibship size (n)*	No. of sibships (x)	(q')(n)	Total affected		χ^2 $(o–e)^2/e$
			Expected (q')(n)(x)	Observed	
1	1	1	1	1	0.000
2	3	1.143	3.429	5	0.720
3	1	1.297	1.297	1	0.068
6	2	1.825	3.65	4	0.034
9	1	2.433	2.433	1	0.844
11	1	2.871	2.871	3	0.006
Total	9		14.68	15	1.671

*Stillbirths and miscarriages were not included when determining sibship size and the number of unaffected siblings. χ^2 with 4 degrees of freedom = 1.671, $P > 0.80$ demonstrates that there was no significant difference between the number of affected observed and expected, assuming complete truncate ascertainment.

found (Fig. 2I), while in the paler areas there were often small trilaminar fragments.

Renal pathology

Renal biopsy specimens of two German (P13 and P15) and one Australian patient (P02) were available. All three patients had focal glomerulosclerosis, with features of collapsing glomerulopathy evident in two of these (P02 and P13) (Fig. 3). One of the two German patients (P13) showed patterns of both collapse and hyalinosis/sclerosis. The other German patient (P15) showed a pattern of segmental sclerosis/hyalinosis alone. Limited material was available for review from an original French Canadian patient (P07); there was evidence of focal glomerulosclerosis, but features of collapsing glomerulopathy were not seen.

Discussion

AMRF is a distinctive form of progressive myoclonus epilepsy that can be diagnosed clinically and is inherited as an autosomal recessive trait (Table 2). From a neurological point of view, tremor as an early feature should raise a suspicion of the condition. Unlike most progressive myoclonus epilepsies, intellect is remarkably preserved in this disorder. This may relate to the fact that storage is not intraneuronal, as it is in many other forms of progressive myoclonus epilepsy (Berkovic *et al*., 1986, 1993). Suspicion of this disorder should also be raised by the presence of proteinuria and progressive renal impairment in an adolescent or young adult with myoclonus epilepsy.

The clinical spectrum in this series demonstrates that AMRF can present with either renal or neurological features, typically at the end of the second decade, but with a range between 9 and 25 years. Tremor and progressively disabling multifocal action myoclonus with infrequent tonic–clonic seizures and cerebellar features are characteristic. The absence of dementia is striking. This perspective, from a study of 15 cases, confirms and extends the phenotype initially described in four French Canadian patients (Andermann *et al*., 1986). Clinical peripheral neuropathy was absent, but electrophysiological

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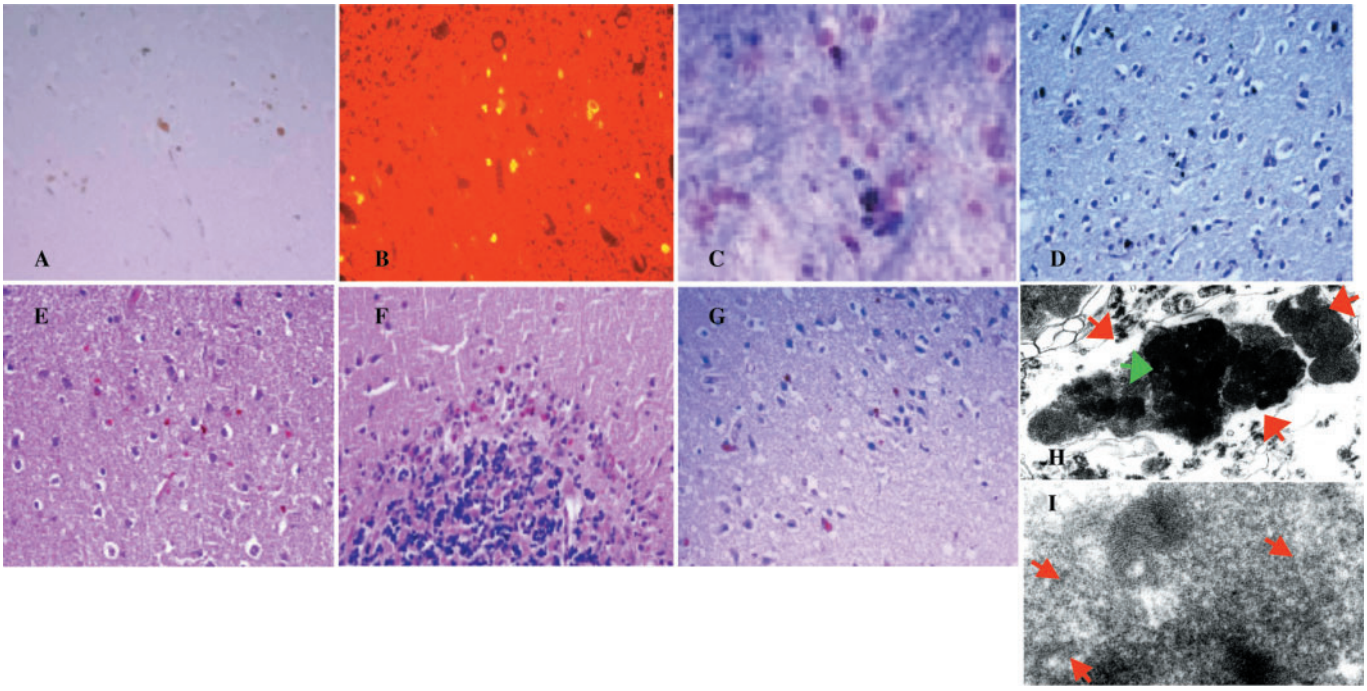

Fig. 2 Neuropathology: autopsy of patient P02. (**A**) Unstained deparaffinized section of cerebral cortex showing granules of golden brown pigment (× 200). (**B**) An unstained deparaffinized section of cerebral cortex shows the autofluorescence of the pigment granules (× 200, wavelength 550 nm) which resembles that of lipofuscin. (**C**) Pigment granules, located in the neuropil of the outer layers of the cerebral cortex, stain with Sudan black (× 400). This fact and the fact that they persist in paraffin sections (which have been through lipid solvents) suggests that their main component is a lipoprotein or proteolipid. (**D**) Pigment granules in cerebral cortex stain blue–black with Luxol fast blue (LFB). In contrast, lipofuscin does not stain with LFB on carefully differentiated sections (× 200). (**E**) Haematoxylin and eosin-stained section of cerebral cortex in which pigment granules appear golden brown (× 200). (**F**) Haematoxylin and eosin-stained section of cerebral cortex showing extracellular accumulation of pigment in the layer of Bergman glia. No pigment is present in Purkinje cells (× 200). (**G**) Section of cerebral cortex stained with periodic acid–Schiff (PAS). Extracellular pigment appears orange–brown (× 200). (**H**) This relatively low-power electron micrograph from the cerebellum in the region of the Bergmann astrocytes shows a characteristic deposit. Note the mulberry-like contours, suggesting that it was formed by concretion of globules ∼0.6 μm in diameter. The electron density is variable. A membrane surrounds the deposit on some sides (red solid arrow). This suggests that it is intracellular. The green arrow indicates the area illustrated in **I** (× 28 000). (**I**) At high magnification, stacks of lamellae can be seen in some of the denser areas. The periodicity is ∼8 nm. Aside from this, occasional fragments of lamellae are encountered in granular-appearing areas (arrows). The presence of a relatively consistent lamellar pattern distinguishes the granules from banal lipofuscin. The pattern is also different from that of any type of ceroid lipofuscinosis (× 135 000).

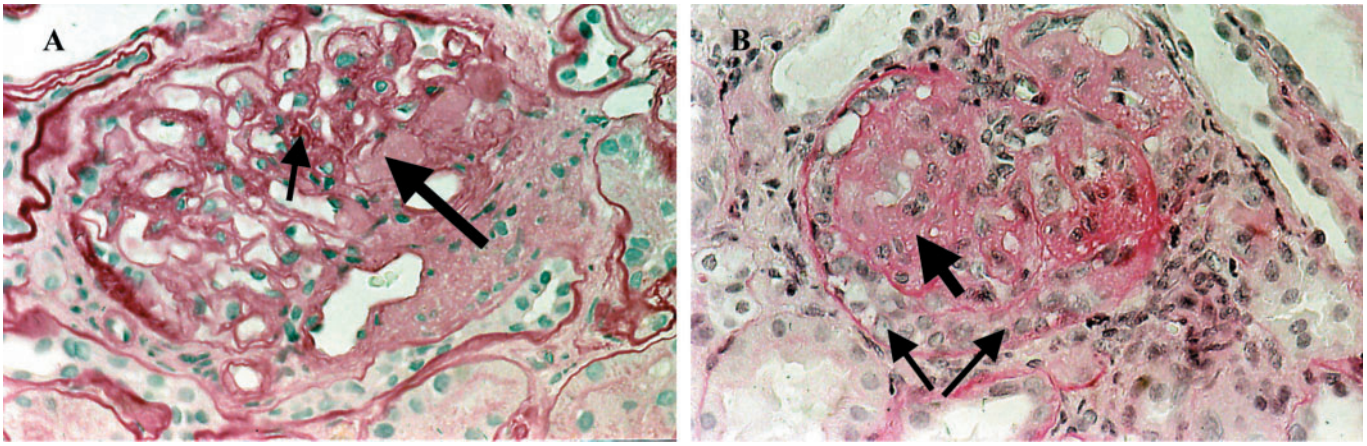

Fig. 3 Renal pathology. Two glomeruli from a German patient (P13) (PAS, original magnification × 400). (**A**) Features of focal glomerulosclerosis with the hyalinosis/sclerosis pattern (thick arrow, hyaline material; thin arrow, sclerosis related to increased mesangial matrix). (**B**) Capillary collapse (thick arrow) and visceral epithelial cell swelling and hyperplasia (thin arrows).

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evidence of neuropathy was observed in one family; this may relate to uraemic neuropathy (Ahonen, 1981) rather than being a core feature of the neurological phenotype.

Superficially, in patients with advanced renal disease, one might confuse this syndrome with uraemic encephalopathy (Mahoney and Arieff, 1982; Lockwood, 1989). However, the clinical picture of AMRF is different, with a clear sensorium and lack of improvement in neurological features with dialysis or transplantation. Moreover, the facts that the neurological manifestations precede renal involvement in about one-third of the cases, and a specific form of storage material is present in the brain, clearly distinguish AMRF from uraemic encephalopathy.

The age of onset of this disorder (adolescent to young adult) may raise the question of Kufs' disease (Berkovic *et al*., 1988). AMRF differs clinically from Kufs' disease by the absence of dementia and by the associated renal involvement. The storage material observed in brain could lead to a pathological misdiagnosis of Kufs' disease. However, as previously pointed out, the storage in AMRF is extraneuronal, whereas in Kufs' disease there is prominent intraneuronal storage (Carpenter *et al*., 1977).

The brain histological and electron microscopic features of the Australian case described here were identical to those of the previously published Canadian patient (Andermann *et al*., 1986). The pigment accumulated in AMRF, which has yet to be characterized biochemically, is likely to be lipofuscin-like oxidized lipid or proteolipid based on its staining characteristics. It has different ultrastructural characteristics from those observed in Kufs' disease. The pigment is extraneuronal, in astrocytes or in the extracellular space, and there is no increase in intraneuronal lipofuscin. The contribution of chronic dialysis to a heightened state of lipid peroxidation may have a role in the pathogenesis of the pigment formation, as the use of vitamin E and other antioxidants in dialysis patients is a relatively recent practice. No such pigment has been observed so far in the renal biopsies.

The clinical tempo of this disorder varies somewhat within and between families. The first clinical symptoms can be renal or neurological. The progression of neurological and renal disorders appears to be separate. We interpret these findings to indicate that the unitary molecular lesion has pleiotropic effects, differentially affecting the two organ systems.

The initial description of this disorder was only in French Canadians, suggesting that it might be confined to this isolate. The current study demonstrates that this syndrome has a more extensive ethnic and geographic distribution, and we suspect that it is probably under-recognized. It is possible that cases with a predominantly renal presentation and later neurological disease are misdiagnosed as uraemic encephalopathy.

In progressive myoclonus epilepsies, there is presumably a unique physiological system involved, leading to the characteristic cortical (and sometimes subcortical) myoclonus, tonic–clonic seizures and ataxia. The specific identity of this system is currently unknown. However, it appears vulnerable to processes that involve intraneuronal storage (e.g. Lafora disease, ceroid lipofuscinoses, sialidosis), conditions that lead to neuronal degeneration via a number of mechanisms (Unverricht–Lundborg disease, MERRF, DRPLA), and now storage of extraneuronal material in AMRF can be added to this list. A fine rhythmic tremor as an early clinical feature of progressive myoclonus epilepsy is unusual. It could actually represent a form of cortical myoclonus, as has been described in benign familial adult myoclonic epilepsy (Sano *et al*., 2002), but detailed electrophysiological studies to test this in AMRF have not been done.

In the original description of AMRF, the renal pathology showed focal glomerulosclerosis in all four patients, with interstitial fibrosis in three of four patients (Andermann *et al*., 1986). Collapsing glomerulopathy appears to be typical in AMRF, and this is regarded as a severe variant of focal glomerulosclerosis (Detwiler *et al*., 1994; Meyrier, 1999). Collapsing glomerulopathy has been associated with hepatitis C, human immunodeficiency virus, autoimmune diseases and lymphoproliferative disorders, but is often idiopathic (Detwiler *et al*., 1994; Grcevska and Polenakovik, 1999; Laurinavicius *et al*., 1999; Meyrier, 1999; Singh *et al*., 2000). Familial cases have been mentioned briefly in the literature, and one family with probable recessive inheritance has been described recently (Avila-Casado *et al*., 2003). It now appears that AMRF represents a recessive form of collapsing glomerulopathy.

Focal glomerulosclerosis was previously thought to be sporadic, but recently many familial cases have been identified (Conlon *et al*., 1999). There is genetic heterogeneity, with both autosomal recessive types that usually present in childhood and autosomal dominant forms in adult life (Fuchshuber and Mehls, 2000; Kaplan and Pollak, 2001). Early childhood recessive forms include the congenital nephrotic syndrome of Finnish type due to mutations in the gene encoding nephrin on chromosome 19q (Kestila *et al*., 1998), and steroid-resistant nephrotic syndrome due to mutations in *NPHS2*, a gene encoding the glomerular protein podocin on chromosome 1q (Boute *et al*., 2000). Recessive mutations of the Wilms tumour gene (*WT1*) on chromosome 11 are usually associated with diffuse mesangial sclerosis, but focal segmental glomerulosclerosis is also seen. These patients may have Wilms tumour, male pseudo-hermaphroditism or other genital anomalies (Fuchshuber and Mehls, 2000). Five autosomal dominant loci are known. In some families, focal glomerulosclerosis is due to mutations in α-*actinin 4* on chromosome 19q (Kaplan *et al*., 2000); other families map to chromosomes 11q21–q22 (Winn *et al*., 1999), 1q25–q31 (Tsukaguchi *et al*., 2000), 11q24 (Prakash *et al*., 2003) and 9q31–q32 (Chung *et al*., 2003), but the genes await identification. The genes identified for focal glomerulosclerosis are thus candidates for AMRF.

What is remarkable in AMRF is that there is no visible storage in the kidney, yet there is prominent storage in the brain. Genes identified for glomerulopathies to date have been involved with the glomerular basement membrane and related proteins. We hypothesize that in this autosomal recessive disorder, the mutant protein is also expressed in the brain,

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but cannot be cleared effectively, leading to the peculiar form of brain storage.

In summary, it is important to recognize this condition and to treat the patients in a timely fashion with dialysis and renal transplantation since they can survive for a number of years with retained intellect. More effective treatment of myoclonus with drugs such as piracetam (Fedi *et al*., 2001) may improve their quality of life.

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