# The National Amyloidosis Centre, Royal Free Hospital and UCL, London

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The National Amyloidosis Centre (NAC) is a wholly integrated clinic and research facility located in the Royal Free Hospital and University College London (UCL). The NAC has been at the cutting edge of research and treatment into all aspects of amyloidosis for over 30 years, and since 1999 has been commissioned by the UK National Health Service to deliver a national highly specialised clinical service.

Research in the centre ranges from molecular, genetic, biochemical, physiological, experimental and pathologic investigations through to new clinical diagnostics, improved patient management and drug discovery. There are extensive collaborative links with scientists, clinicians and industry in many of these areas. The core research mission is to elucidate fundamental pathobiological mechanisms in order to improve diagnosis, management and outcome of amyloidosis. The centre has further interests in autoinflammatory diseases as well as the major common diseases associated with local amyloid deposition: Alzheimer's disease and type 2 diabetes mellitus.

The multidisciplinary clinical service is delivered by specialists in rheumatology, immunology, nephrology, neurology and cardiology. Development and refinement of clinical imaging to enable non-invasive diagnosis, quantitation and monitoring of amyloid has been a constant theme over the decades, notably including I123-labelled serum amyloid p ($I^{123}$-SAP) scintigraphy (Figure 1),[1] cardiac $^{99m}$Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) scintigraphy[2] and multiparametric cardiovascular magnetic resonance (CMR)[3] (Figure 2).

The NAC's amyloidosis practice is the world's largest and most diverse, with a current referral rate of 1,400 new patients per year from the UK and internationally. The clinical service dates back to 1987 when Professors Sir Mark Pepys and Philip Hawkins developed $I^{123}$-SAP scintigraphy for diagnosis of amyloidosis.[1] The $I^{123}$-SAP scintigraphy tracer localises quantitatively to amyloid deposits throughout the body producing diagnostic images in patients with systemic amyloidosis; follow-up whole body scans quantitatively track amyloid burden in solid viscera.[4] Contrary to previous expectations, $I^{123}$-SAP scintigraphy has systematically shown that amyloid deposits exist in a state of dynamic turnover, and that they gradually regress in many patients in whom the underlying cause is suppressed (figure 1).[4] $I^{123}$-SAP scintigraphy has been a core investigation in patients attending the NAC for 32 years, with more than 35,000 scans having been performed. Systemic demonstration of amyloid regression following treatment that suppresses production of the respective amyloid fibril precursor proteins in AA, light chain (AL) and various other types of amyloidosis has greatly encouraged much more active approaches to therapy, including cytokine blocking anti-inflammatory treatment and novel chemotherapy in acquired AA and AL amyloidosis respectively, to liver transplantation in hereditary amyloidosis, and most recently highly effective small interfering RNA and antisense oligonucleotide gene silencing therapies in familial forms of transthyretin (ATTR) amyloidosis.

ATTR amyloidosis was until recently considered to be a rare and untreatable cause of heart failure in older people, diagnosis of which required invasive endomyocardial biopsies. Research at NAC led by Professor Julian Gillmore has shed important insights into its pathogenesis and genetic susceptibility; validated non-biopsy diagnosis using repurposed bone scintigraphy, a widely available medical imaging technology;[2] elucidated the clinical phenotype and natural history of the disease; and in collaboration with Alnylam Pharmaceuticals Inc and Akcea Therapeutics Inc has contributed to development of novel highly effective gene silencing therapies that have lately entered the clinic worldwide.[5,6] Awareness of the disorder and referrals of patients with ATTR amyloidosis to NAC have increased exponentially due to the imaging innovations; we evaluated more than 250 new patients with ATTR amyloidosis last year and believe this may be the tip of the iceberg.

Other work on ATTR amyloid at NAC has elucidated a novel mechano-enzymatic pathway for its pathogenesis that has identified new therapeutic targets;[7] created the first transgenic mouse model of cardiac ATTR amyloidosis; characterized many novel mutations that cause rare hereditary forms of the disease; developed a simple but robust clinical staging method using blood biomarkers, which enables estimation of prognosis and stratification of patients for clinical trials[8].

Studies in NAC led by Dr Marianna Fontana have developed and validated multiparametric CMR as a remarkably discerning and informative tool in amyloidosis, which is now the cornerstone for characterizing cardiac involvement in all types of systemic amyloidosis.[9-12] CMR enables assessment of cardiac structure and function far more accurately than echocardiography, but its unique advantage in amyloidosis is its ability to provide information about tissue composition, i.e. myocardial tissue characterization (figure 2).

CMR can identify and quantify differences in the intrinsic contrast of the myocardium in health and disease without the use of gadolinium contrast, since pathology changes the intrinsic myocardial magnetic properties referred to as T1, T2 and T2* measurements. Intravenous administration of contrast media facilitates the late gadolinium enhancement technique (LGE) and extracellular volume (ECV) mapping. Our seminal study with the Royal Brompton Hospital in 2005 reported the pathognomonic appearance of LGE imaging in cardiac amyloidosis[13], which triggered wide interest in the application and many new CMR developments that have substantially diminished need for cardiac biopsies.

The CMR parameters of native T1 and ECV elegantly map the continuum of cardiac amyloid deposition from its earliest to latest stages, correlating with amyloid burden and providing incremental information on prognosis[10,11,14]. The unique ability to serially quantify cardiac amyloid deposits by CMR through T1 mapping has huge potential to redefine response to treatments in all types of cardiac amyloidosis.[3] Very encouragingly, and once again in contrast to expectations, we have lately shown that chemotherapy in AL amyloidosis is often associated with improvements in T1, ECV and LGE parameters, i.e. regression of cardiac AL amyloid, over periods as little as 6 months.[12] This has important implications for the duration and intensity of chemotherapy required in individual patients. The development of immunotherapies to promote clearance of amyloid, including the work of Professor Sir Mark Pepys in our centre, is well advanced[15,16] and the ability to serially measure changes in cardiac amyloid load by CMR provides a novel endpoint for early stage drug development and dose ranging. CMR studies have thus shed new light on the pathophysiology and natural

turnover of cardiac amyloid, highlighting its dynamic nature; this encourages development of ever more effective and rapidly acting therapies to suppress amyloid precursor protein production along with treatments to remove existing amyloid deposits.

Our CMR studies have also characterized additional pathologic mechanisms that are likely to contribute to disease progression beyond just the amyloid burden. Native T2 is a specific measure of myocardial oedema, which causes T2 to increase. T2 is elevated in cardiac amyloidosis and histological correlation demonstrates the presence of oedema in the absence of any significant inflammatory infiltrate.[12] Oedema is present more frequently and prominently in AL compared to ATTR amyloidosis, cardiac AL type thus representing a spectrum characterized by variable degrees of amyloid infiltration (measured with LGE, T1 and ECV) along with superimposed myocardial oedema (T2). ECV and T2 measurements therefore define separate processes that independently contribute to the clinical picture.

CMR evaluation of structure, function and tissue characterization (LGE and T1, T2 and ECV mapping) is redefining cardiac amyloidosis by separating the different myocardial processes, ranging from amyloid infiltration to oedema and myocyte response.[12] This work is driving a paradigm shift in understanding the pathobiology of cardiac amyloidosis, informing and enabling future research on the mechanisms and effects of the many therapies in current use and in development.

# References


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## Figures

**Figure 1**. Anterior whole body $^{123}$I-labelled SAP scans taken 10 years apart in a patient with systemic AL amyloidosis who was treated with systemic chemotherapy. The baseline scan (left) shows a large visceral amyloid load in the liver and spleen which has completely regressed on the later scan (right).

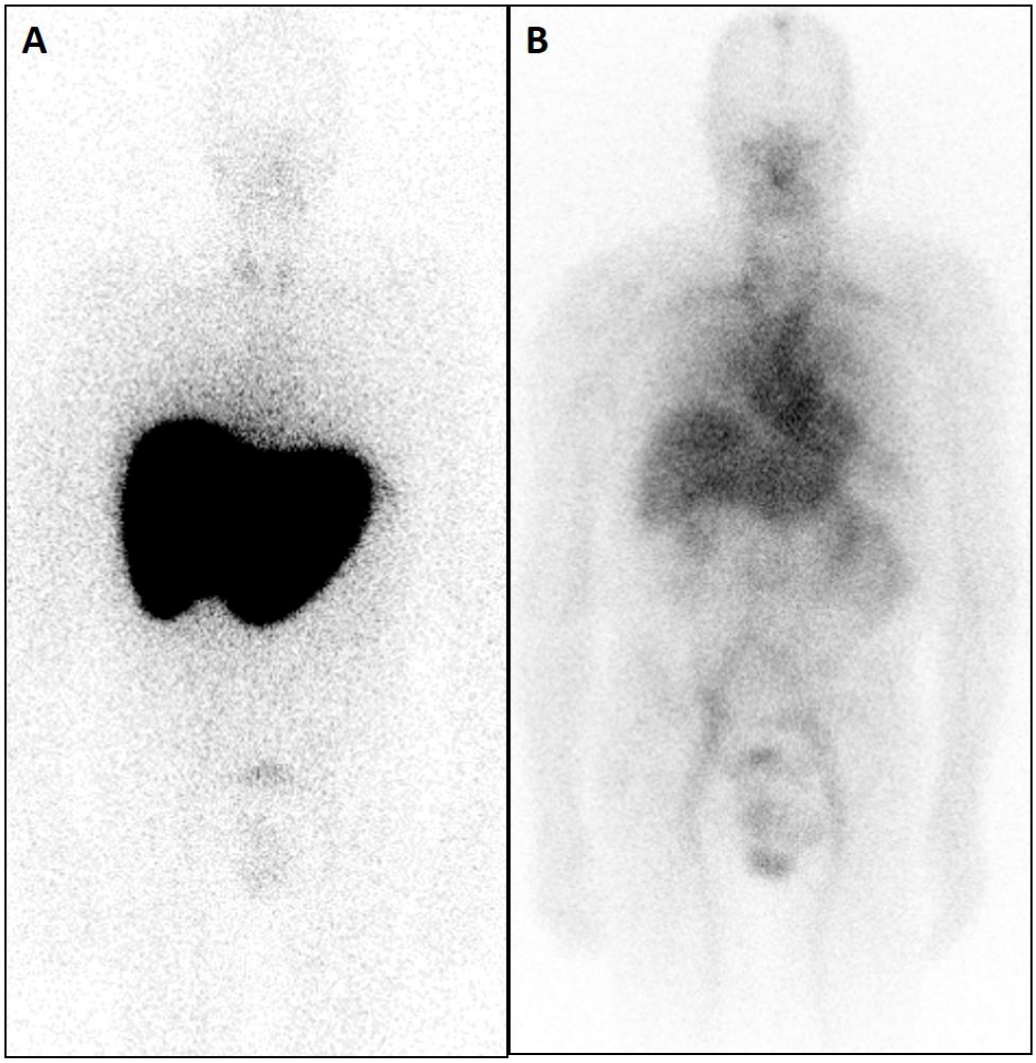

**Figure 2.** This multidisciplinary workup of a patient with wild type cardiac transthyretin amyloidosis (A) a strain pattern characteristic of an infiltrative process; (B) a 4-chamber cine steady-state free precession image, corresponding non contrast T1 map, LGE image showing transmural LGE and ECV map; and (C) whole-body anterior 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy and hybrid single-photon emission computed tomography-computed tomography showing Perugini grade 2 abnormal uptake.