This scientific commentary refers to ‘Clinical features and autonomic testing predict survival in multiple system atrophy’ by Coon et al. (doi:10.1093/awv274).

Multiple system atrophy (MSA) is a progressive neurodegenerative disease that affects 3–5 people out of every 100,000 in the general population (Gilman et al., 2008). It is characterized by a varying combination of parkinsonian, cerebellar, pyramidal and autonomic symptoms. The latter include orthostatic hypotension and bladder, bowel, sexual and breathing disorders. The clinical abnormalities are due to a complex pathophysiology that reflects neurodegeneration of cortical areas, the basal ganglia, brainstem and cerebellum (Trojanowski and Revesz, 2007; Gilman et al., 2008; Bologna et al., 2014; Suppa et al., 2014). Widespread neuronal degeneration results in a short median survival time, ranging across studies from 6 to 9 years (Wenning et al., 2004).

With no known biomarkers for disease diagnosis or progression, clinicians and scientists have long recognized the importance of classifying MSA into distinct subtypes to be able to identify features that influence the rate of progression and response to interventions. Two main disease subtypes are recognized: (i) patients with predominantly parkinsonian features are said to have MSA-Parkinsonism (MSA-P); and (ii) patients with predominantly cerebellar ataxia are said to have MSA-Cerebellar (MSA-C). Clinical features of autonomic involvement are present in both cases, although their severity varies. Autonomic failure in MSA is caused by pathology of the medullar and spinal autonomic nuclei, which invariably display neuronal loss and the presence of α-synuclein immunoreactive glial and neuronal cytoplasmic inclusions.

With regard to the natural history of the disease, whether there are any differences between the MSA-P and MSA-C subtypes remains a matter of debate (Wenning et al., 2004). There is also controversy over the role of autonomic disorders as predictors of a more aggressive form of MSA, with some studies showing that early or initial autonomic symptoms are associated with worse survival (Wenning et al., 2013; Low et al., 2015), while others have been unable to replicate this association (Roncevic et al., 2014). In this issue of Brain, Coon and co-workers investigate the role of autonomic testing as a means of evaluating survival in patients with MSA and conclude that the results of such tests can indeed serve as a prognostic marker (Coon et al., 2015).

Between January 1998 and December 2012, Coon and colleagues evaluated a large number of patients (n = 685) and then retrospectively reviewed them for the current study; 594 met the consensus criteria for probable MSA, and the remaining 91 for possible MSA (Gilman et al., 2008). MSA-P was the predominant subtype, found in 430 patients (63%). Median disease duration from symptom onset to death was 7.5 years. Although the retrospective nature of this study to some extent limits interpretation of the results, the study does comprise the largest published cohort of patients examined and diagnosed at a single referral centre. In addition, the validity of the study was further strengthened by the fact that the diagnosis of MSA was neuropathologically confirmed in all 36 patients who were examined post-mortem. Lastly, all patients underwent comprehensive and standardized autonomic testing, including the sudomotor axon reflex, heart rate response to deep breathing, blood pressure responses to the Valsalva manoeuvre and head-up tilting.

Coon and co-workers used multivariate analysis to identify clinical predictors of shortened survival; six variables were included in the final model as independent predictors of shortened survival, the strongest being falls occurring within 3 years of symptom onset. However, four of the other five independent predictors were related to autonomic symptoms (orthostatic intolerance, bladder symptoms and early catheterization) or the general degree of autonomic impairment evaluated by means of a specific and validated scale, the Composite Autonomic Severity Score (Suarez et al., 1999). Later age of onset was the remaining negative

© The Author (2015). Published by Oxford University Press on behalf of the Guarantors of Brain. All rights reserved.
For Permissions, please email: journals.permissions@oup.com
predictor of survival. Coon et al. also analysed the role of motor phenotypes. As age at onset was greater in the MSA-P than the MSA-C subtype, the analysis of overall survival in each subtype was adjusted for this, but no differences emerged.

The finding that early and generalized autonomic dysfunction over the disease course, though not the prevalent motor phenotype, is associated with shorter survival in MSA underscores the importance of standardized autonomic testing not only as a means of identifying this disease but also as an important prognostic indicator. Technical advances have been made in this regard (Baschieri et al., 2015); one such example can be seen in a large multicentre European study on orthostatic hypotension in patients with MSA, in which a prolonged 10-min orthostatic challenge was shown to substantially increase sensitivity in detecting orthostatic hypotension (Pavy-Le Traon et al., 2015). This ‘extended’ cardiovascular testing should thus be recommended when studying cases with suspected MSA.

In addition, the early identification of autonomic involvement using standardized testing has important implications for the neurologist who attends to such patients since it allows appropriate symptomatic treatments to be planned promptly (Colosimo et al., 2005); management strategies are available for the vast majority of autonomic disorders associated with MSA, including cardiovascular, genitourinary and respiratory symptoms, and may provide significant benefits for patients.

Full credit should now be given to the two American physicians, Milton Shy and Glenn Drager (Fig. 1), who more than 50 years ago described a novel progressive neurological syndrome associated with severe orthostatic hypotension, later named Shy–Drager syndrome. In their seminal paper they had already pointed out that ‘a primary degenerative nervous system disorder may be one etiological factor in orthostatic hypotension’ and that ‘it would appear that this is a recognizable clinical and pathological syndrome’ (Shy and Drager, 1960).

Carlo Colosimo1 and Alfredo Berardelli2
1 Department of Neurology and Psychiatry, University of Rome “Sapienza”
2 IRCCS Neuromed and Department of Neurology and Psychiatry, University of Rome “Sapienza”

Correspondence to: Alfredo Berardelli
E-mail: alfredo.berardelli@uniroma1.it
doi:10.1093/brain/awv303

Figure 1 (A) George Milton Shy (1919–67) and (B) Glenn Albert Drager (1917–67). Reprinted from Encyclopedia of Movement Disorders, Vol. 3, Kompoliti and Verhagen-Meetman, pp.111–114, 2010, with permission from Academic Press.

References


Trojanowski JQ, Revesz T. Proposed neuropathological criteria for the post mortem diagnosis of multiple system atrophy; Neuropathology Working Group on
New insights into acquired temozolomide resistance in glioblastoma?

This scientific commentary refers to ‘c-Myc–miR-29c–REV3L signalling pathway drives the acquisition of temozolomide resistance in glioblastoma’ by Luo et al. (doi:10.1093/brain/awv287)

The emergence of tumour cell resistance to chemotherapy represents a major challenge for the development of durable therapeutic strategies across most solid cancers including glioblastoma, the most malignant primary brain tumour in adults. The standard of care for glioblastoma is maximum surgery as safely feasible followed by radiotherapy, with concomitant and maintenance chemotherapy with the alkylating agent temozolomide (TMZ/RT→TMZ). This results in a median overall survival in the range of 12 months on a population level (Weller et al., 2014). Radiotherapy alone doubled median survival in early studies, but the best radiological response is commonly stable disease, progression is inevitable, and the efficacy of radiotherapy may be partly related to anti-angiogenic rather than intrinsic tumour cell cytotoxic effects. Mechanisms underlying resistance to radiotherapy remain poorly understood, but extensive hypoxia may be an important factor.

TMZ was approved for the treatment of newly diagnosed glioblastoma because of a moderate prolongation of median survival (Stupp et al., 2005). Subgroup analyses revealed that the benefit from TMZ was largely restricted to patients with glioblastomas that exhibit a particular epigenetic alteration, promoter methylation of the O6-methylguanine DNA methyltransferase (MGMT) gene (Hegi et al., 2005). However, even these patients eventually all progress and succumb to their disease, in the absence of changes in MGMT promoter methylation (Felsberg et al., 2011), indicating that novel pathways must be activated to escape from alkylating agent chemotherapy.

Considerable efforts have been made to understand and overcome glioma cell resistance to chemotherapy, focusing on several proteins and pathways involved in cell survival and resistance, including the mismatch repair (MMR) pathway. In this issue of Brain, Luo and co-workers report that a c-Myc driven downregulation of microRNA (miR)-29c promotes a TMZ-resistant phenotype of glioma cells that is mediated by increased REV3L expression and consequent enhanced DNA repair capacity (Luo et al., 2015).

MicroRNAs have been studied extensively over the last decade for their role in diverse biological processes, especially in cell proliferation and cell death. These small non-coding RNA molecules can affect post-transcriptional control of gene expression and may thereby help to regulate several aspects of tumorigenesis, including invasiveness, DNA repair, and acquired resistance to genotoxic cancer therapy. MicroRNAs can function as either tumour suppressors or promoters, in a context-dependent manner. While downregulation of miR-29c has been associated with tumorigenesis and invasiveness in a variety of cancers, including gliomas (Fan et al., 2013; Wang et al., 2013), no link to TMZ resistance has been established so far.

Here, Luo and co-workers used quantitative PCR and in situ hybridization to confirm a downregulation of miR-29c—which was selected from an array-based analysis of matched primary and recurrent human gliomas considered TMZ-resistant—in recurrent tumour samples and cell lines selected for TMZ resistance (U251/TMZR, U87/TMZR). Restoration of miR-29c expression restored TMZ sensitivity. By contrast, inhibition of miR-29c in A172 cells, which express high levels of miR-29c comparable to those of normal human astrocytes, conferred TMZ resistance. These effects were reproduced in an in vivo model of non-obese diabetic (NOD)-severe combined immunodeficiency (SCID) mice injected subcutaneously with resistant U251/TMZR cells. Prolonged survival was noted in animals treated with intraperitoneal TMZ at 20 mg/kg and simultaneous intratumoural injection of miR-29c (1 nmol), applied as cholesterol-conjugated 2'-O-methylmodified miR-29c for better pharmacokinetic properties.

To assess potential target genes that could be mediating the effect of miR-29c, Luo et al. used a somewhat artificial or at least unconventional approach: they generated a list of candidate genes that were (i) deregulated in TMZ-resistant cell lines that had been engineered to overexpress miR-29c; and (ii) also predicted targets of miR-29c according to public databases. They identified REV3L, a DNA repair polymerase previously