LETTER TO THE EDITOR

Ravel’s last illness: a unifying hypothesis

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The neurological illness of Maurice Ravel continues to attract speculation and controversy, as exemplified by recent contributions to Brain (Sellal, 2008; Seeley et al., 2008). While the true diagnosis will never be known, the detailed documentary evidence provided by his neurologist Théophile Alajouanine (1948) and in contemporary correspondence (Larner, 1996) allows the key features of his case to be reconstructed. Ravel developed insidiously progressive apraxia and aphasia in late middle life, accompanied by impaired musical expression, but retained understanding of music and a number of other intellectual functions. The total duration of the clinical disorder is difficult to establish but probably of the order of 5 years. Ravel’s language disorder was characterized by Alajouanine as a ‘Wernicke’s aphasia’, with prominent anomia, agraphia and alexia (for both verbal and musical material). He was noted to be apathetic and withdrawn later in the course of the illness. Other neurological (in particular, extrapyramidal) or behavioural features were not emphasized. Since neuroimaging techniques were not available and no necropsy was performed, the pathological anatomy cannot be defined precisely; however, the clinical syndrome suggests a focal cortical dementia involving the dominant hemisphere with prominent parietal damage. The operation notes from the craniotomy performed just prior to Ravel’s death indicate that the right hemisphere was atrophic suggesting that the pathological process may have been asymmetrical, though Alajouanine’s own notes do not corroborate this (Alajouanine, 1948). There is an additional suggestion of a family history. Ravel’s father developed a neurological illness in later life associated with waning of intellect: although this has sometimes been attributed to a cerebral thrombosis, deficits apparently progressed for at least 2 years prior to death (Larner, 1996).

Debate concerning Ravel’s diagnosis has been fuelled by the confused nomenclature and nosology of frontotemporal lobar degeneration (FTLD), primary progressive aphasia (PPA), so-called ‘progressive apraxia’ and the corticobasal syndrome (CBS). While the spectrum of deficits associated with PPA is not restricted to the domain of language, the significance and time course of non-language impairments remain unresolved issues. The clinical syndromes are underpinned by a wide and heterogeneous spectrum of histopathological findings (Cairns et al., 2007). The growing use of the term CBS reflects the poor correlation between clinical and pathological phenotype in corticobasal degeneration (Boeve et al., 2003) and PPA is also more appropriately regarded as a syndrome rather than a discrete entity. Furthermore, those syndromes of PPA and CBS themselves overlap and share histopathological substrates (McMonagle et al., 2006; Josephs et al., 2006).

Recent advances in our understanding of the molecular basis of PPA and CBS may help to resolve this nosological impasse, and suggest an alternative unifying solution to the vexed question of Ravel’s diagnosis. It is now recognized that mutations in the progranulin (GRN) gene produce clinical phenotypes that include elements of both PPA and CBS (Gijselinck et al., 2008). This entity appears to be common, accounting for up to ~10% of all cases of FTLD across series (Gijselinck et al., 2008). We propose that Ravel may have had a cerebral TDP43opathy on the basis of a GRN mutation. Certain features of the progranulinopathy spectrum would fit Ravel’s clinical syndrome (Beck et al., 2008; Gijselinck et al., 2008); besides prominent apraxia and other parietal deficits, these patients may have progressive aphasia dominated by anomia as well as apathy without other significant behavioural changes. Other neurological signs are usually less salient and develop in fewer than half this group. Cerebral atrophy may be markedly asymmetric. Onset of disease is usually in late middle life with mean disease duration around 5 years. A positive (autosomal dominant pattern) family history is usual but ‘sporadic’ cases have been described, probably reflecting age-related disease penetrance. If indeed Ravel had a progranulinopathy, his case would extend the phenotype of this molecular brain lesion to embrace some of the most cherished artefacts of the human imagination.
References

Sellal F. A few comments on Ravel’s disease. Brain [Epub ahead of print, June 30, 2008].