In 1911, the Spanish neurologist-pathologist Gonzalo Lafora, working at the then Government Hospital for the Insane in Washington DC, first described the progressive myoclonus epilepsy that would later bear his name (Lafora, 1911). The journey to understand this disease started with Lafora’s detailed neuropathological description of the large and profuse inclusions (Fig. 1) that would come to be known as Lafora bodies. The odyssey has visited many a shore, and the latest and most mysterious is revealed by Javier Gayarre et al. (2014) in this issue of Brain.

Whereas the ‘amyloid’ plaques of Alzheimer’s disease are not in fact amyloid (starch), Lafora bodies, by contrast, are. Lafora bodies are composed of hyperphosphorylated and malformed glycogen molecules. These abnormal starch-like polyglucosans aggregate to form insoluble masses, which over time accumulate inside neuronal somata and dendrites.

Lafora disease is caused by loss-of-function mutations in the EPM2A (laforin) or EPM2B (malin) genes (Minassian et al., 1998; Chan et al., 2003). Laforin is the only known glycogen phosphatase. Its absence leads to hyperphosphorylation of glycogen, which correlates with a gradual accumulation of polyglucosans, strongly suggesting that glycogen hyperphosphorylation underlies polyglucosan formation (Tagliabracci et al., 2008). Laforin’s structure resembles that of the plant starch phosphatase SEX4, which is crucial to starch metabolism; its absence leading to a pathological excess of starch. Laforin complements SEX4 and rescues the starch-excess phenotype of SEX4-deficient plants (Gentry et al., 2007). The phosphatase activity of laforin is its only known enzymatic function. Together, these findings suggest a central role for impaired glycogen dephosphorylation by laforin in Lafora disease pathogenesis. As for the enzyme behind glycogen phosphorylation, despite many efforts to identify it, that shore remains unattained.

Malin, meanwhile, has been shown to be a ubiquitin E3 ligase. Paradoxically, malin’s only unequivocal target for proteasomal degradation turns out to be none other than laforin (Gentry et al., 2005). How can the absence of malin lead to the same disease as does absence of the protein, laforin, that malin destroys? A solution to this conundrum was suggested by recent work which revealed that, in the absence of malin, laforin accumulates in glycogen and may thus disturb the spherical architecture that is essential for glycogen’s solubility (Tiberia et al., 2012). As such, excess phosphate in glycogen (as a result of laforin deficiency) or excess laforin in glycogen (due to malin deficiency) would have the same effect on glycogen, reducing its solubility and leading it to precipitate and form Lafora bodies.

In the current issue of Brain, Gayarre et al. (2014) guide the ship into a new night. They overexpress, in laforin-deficient mice, a form of laforin mutated to lack phosphatase activity, and show that this rescues murine Lafora disease. The inescapable conclusion is that the phosphatase function of laforin is dispensable, and that it is some other function of the laforin-malin complex that is relevant to the disease. The function that Gayarre et al. (2014) highlight, namely autophagy, has been of late a frequent stop in the Lafora voyage, and indeed in the exploration of many other neurodegenerative diseases. Autophagy is disturbed in Lafora disease (Criado et al., 2012), and it has been suggested that defective autophagy impairs the ability of cells to rid themselves of abnormal aggregates, such as malformed glycogen. Gayarre et al. (2014) advance the tantalizing idea that glycogen, in common with proteins, can sometimes be naturally misshapen. This would lead it to precipitate and aggregate, and indeed to accumulate were it not for mechanisms involving laforin and malin that act to clear such deposits. Before accepting autophagy as a port of call of the Lafora saga, one must however keep an open mind. Is it possible that laforin’s sole enzymatic activity is unnecessary?

The vicissitudes of the Lafora epic will certainly continue to lead us to exciting lands of milk and honey most relevant to the understanding of neuronal function. But what of the patients who suffer the intractable and continuous seizures, hallucinations and dementia of Lafora disease? The polyglucosans that cause havoc in Lafora disease, irrespective of their shape or origins, are in the end nothing more than chains of glucose. One and only one enzyme, glycogen synthase, manufactures chains of glucose, and recent studies have shown that downregulation of glycogen synthesis prevents Lafora disease in mice (Pederson et al., 2014). While the Lafora pathogenesis ship feels its way through the unknown, a shortcut to safe harbour, namely glycogen synthesis downregulation, may well be open for patients with the disease.
Figure 1  Lafora bodies as drawn by Lafora in his original manuscript (Lafora, 1911).
Gonzalo Lafora would have appreciated the progress made by the explorers so far.

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References


Removing the brakes on post-stroke plasticity drives recovery from the intact hemisphere and spinal cord

The existence of bilaterally redundant corticospinal pathways suggests a potential means of recovery after unilateral injury such as stroke. However, in the adult brain, plasticity is kept in check by inhibitory factors that provide the stability necessary in neuronal networks to encode memories and retain learned actions. In the current issue of Brain, Nicolas Lindau and colleagues use antibodies that block Nogo-A functioning to unlock plasticity within the adult injured brain, leading to a structural and functional re-routing of corticospinal signals to exploit circuit redundancy (Lindau et al., 2014).

After a large motor cortex stroke, there is evidence that the intact hemisphere can control the impaired hand and thus facilitate behavioural recovery (Grefkes and Ward, 2014). However, hemiparesis remains a common deficit after stroke, indicating a need for therapies that augment spontaneous recovery. Lindau et al. (2014) show that, in rats, promoting axonal sprouting by blocking the growth-inhibitor protein Nogo-A facilitates the emergence of motor pathways that allow the intact hemisphere to drive motor output to the impaired forelimb. Although only 10% of corticospinal projections terminated in the ipsilateral spinal cord before injury, anti-Nogo-A therapy induced the generation of additional ipsilateral motor projections and produced substantial recovery of forelimb function.

During the development and refinement of the nervous system there is extensive axonal sprouting. To curb ebullient outgrowth in the adult, various inhibitory molecules such as Nogo-A keep the system in check. Over the years, the Schwab group has systematically examined the therapeutic potential of inhibiting Nogo-A in a number of disease models, including stroke. Initial efforts were aimed at enhancing sprouting at the cortical level through the expression of Nogo-A antibodies in peri-infarct tissue (Emerick et al., 2003). To evaluate a more clinically accessible approach to treatment, Lindau et al. (2014) delivered a Nogo-A inhibitor intrathecally to the lumbar spinal cord. This method builds on