event, and those with medically managed acute coronary syndrome were excluded.

Despite the diagnostic value of PFT, over the past decade, RCTs have failed to show its role in guiding the choice of antiplatelet therapy. In turn, PFT has struggled to find a space in routine clinical practice. The experience from previous studies led to the design of the TROPICAL-ACS trial, the results of which now provide additional insights on how to use PFT to help select a $P2Y_{12}$ inhibitor, thus suggesting a potential resurgence of a nearly abandoned instrument. Future research should build upon TROPICAL-ACS to help to define antiplatelet treatment approaches associated with optimal safety and efficacy performance profiles for the individual patient.

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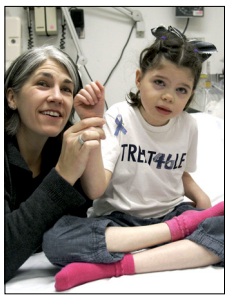
A hopeful therapy for Niemann-Pick C diseases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Niemann-Pick C1 disease (NPC1) is a rare autosomal recessive lysosomal storage disease, which was separated from the sphinomyelinase-deficient NPCA and NPCB when cholesterol was found to be stored.[1] No drugs for the disease are currently approved in the USA, although miglustat is approved in Europe. In *The Lancet*, Daniel Ory and colleagues[2] report strong evidence that intrathecal delivery of hydroxypropyl-beta-cyclodextrin (HPBCD) slows the progression of NPC1.

In this non-randomised, open-label, dose-escalation phase 1/2a study, 14 neurologically affected NPC1 patients were given monthly intrathecal HPBCD doses ranging from 50 mg to 1200 mg. Three additional patients were treated every 2 weeks for 18 months. Ory and colleagues[2] reported no major adverse events, and treated patients showed improved neurological severity scores compared with a historical cohort of 21 NPC1 participants of similar age range, suggesting slowed disease progression. This rate of progression decreased as measured by a multimodal scale, especially for cognition and speech.

Cyclodextrins are used to move cholesterol in or out of cell membranes.[3] In 2001, Camargo and colleagues[4] reported a small but significant effect of HPBCD on slowing neurodegeneration in a mouse model of NPC1. When treatment was started earlier and at higher doses, HPBCD was found to be efficacious in extending survival.[5] Intrathecal delivery to mouse and cat brains was shown to be quite effective in ameliorating the symptoms of the disease.[2] Ory and

colleagues' work extends these studies to human beings.

The findings from Ory and colleagues' study[2] raise many questions. First, is the benefit only from desequestering cholesterol in the cell, allowing more normal cholesterol metabolism, or removal of excess cholesterol? Second, are there particular cells for which the therapy is most important? NPC has been termed juvenile Alzheimer's, another disorder in which cholesterol metabolism is important and in which treatment with HPBCD in animal models has been beneficial.[6] Both diseases share defects of autophagy and activation of microglia. Correction of cholesterol storage in these cells may attenuate the microglial activation, which seems to be a major initiator of autophagic and other destructive pathways causing neurodegeneration in NPC disease.[7]

Third, what is the fate of the cholesterol-laden HPBCD? In one study,[8] the HPBCD-cholesterol complex was slowly cleared while free HPBCD appeared in urine within 24 h. Liu and colleagues[5] found of nearly 2 times increase in acidic sterol (ie, bile acids) output in faeces with HPBCD treatment. Would the cholesterol-laden HPBCD increase lung storage of cholesterol as it passes through the pulmonary capillary bed? This could be important as, in mouse models, systemic delivery of HPBCD did not decrease cholesterol storage in the lung[5,9] and might have made it worse. Pulmonary complications contribute to patient deaths, especially in patients with NPC2.

Better drugs and modes of delivery will certainly be developed. One can envision continuous infusion of HPBCD with a pump as is done with baclofen for spasticity of cerebral origin,[10] and this therapy might also provide increased hope for babies born with NPC1. Whole exome sequencing has become very cheap and could replace biochemical tests for newborn screening, adding NPC1 and NPC2 to the panel. The early diagnosis accompanied by therapy started at pre-symptomatic stages of the disease would be expected to secure better efficacy. This possibility is particularly attractive for cerebellar dysfunction, as it largely anticipates the onset of symptoms. In the mouse, cerebellar morphogenic defects occur near birth and are demonstrated by a small cerebellum at 7 days postnatally. These defects, which are likely to be responsible for the pronounced vulnerability of the cerebellum, are mostly rescued by the HPBCD administration during early post natal life.[11]

Because the full development and functional maturation of the human cerebellum encompasses several years of post natal life, with Purkinje cells reaching adult size only at age 7–9 years,[12] there is a large temporal window for rescuing cholesterol dyshomoeostasis. Of course, the potential toxicity of such early therapy on the developing nervous system would need to be studied, but allowing cholesterol to be more available to many pathways in development might not be dangerous. The study by Ory and colleagues[2] is a major advance in the treatment of this devastating disease and is to be applauded.

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