Hypothalamic hamartoma and epilepsy: the pathway of discovery

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Pathological laughter has been recognized as an epileptic manifestation since the dawn of modern neurology, and is attributed to Trousseau. The association of laughing (gelastic) seizures with hypothalamic hamartoma was clearly described nearly 50 years ago [1], although the probable first case, described as an 'astrocytoma' was published in 1938 [1, 2]. In 1967, Gascon and Lombroso analyzed the issue of gelastic seizures in more detail, and suggested the importance of diencephalic lesions in many cases [3]. The lesions were often not identified on pneumoencephalography and CT scanning, in part because previously there was no high index of suspicion for the presence of such lesions in patients with laughing attacks. However, an important French series documented laughing attacks, with hypothalamic hamartomas, recognized largely by CT scan [4, 5], beginning the more detailed epileptological description of the syndrome. The advent of magnetic resonance imaging greatly facilitated identification of the lesions and resulted in more widespread recognition, clinical characterization and scientific enquiry [6].

Many patients did not have precocious puberty, considered a hallmark of these lesions, but presented with intractable epilepsy. The early onset of gelastic seizures, often in the neonatal period, was then recognized and the appearance, later in the first decade, of generalized spike and wave, tonic attacks, and drop attacks, suggested the presence of a secondary, generalized epileptic process. This emerged as a major feature associated with, and probably responsible for the cognitive and behavioural deterioration, important in the catastrophic epilepsy which some of the children developed [6].

Despite some early observations on resection of the lesion, the origin of the laughing attacks remained obscure. The patients frequently had temporal epileptic abnormalities and even temporal ictal onsets were suggested by surface and depth recording. This led to temporal and occasionally frontal resections, which were uniformly unsuccessful in improving seizure control [7].

A turning point in our understanding of the epilepsy came in the mid-1990s with the recording of epileptic discharges from the hamartoma itself, supported by ictal SPECT observations [8-12]. These data suggested that resection of the lesion should, after all, result in seizure control, hopefully with additional benefits in the areas of behaviour and cognition, and there were a number of anecdotal reports and small case series giving some support to this notion [13]. Many neuro-

surgeons however were, to put it mildly, highly skeptical of such an approach and understandably cautious about operating in an area with important vascular and neural structures. Nevertheless, in the late 1990s, a number of teams began systematic studies, using different surgical approaches, despite the risk of complications. The catastrophic nature of the epilepsy in many patients continued to provide a steady impetus for further attempts at providing confirmation of the benefits of resective, disconnective, or destructive surgical approaches (see further). Pharmacological treatment proved remarkably ineffective, and non-specific approaches such as ketogenic diet, callosotomy, and vagal nerve stimulation produced either marginal or no benefits.

It also became clear that not all patients developed seizures in infancy, that secondary, generalized epilepsy did not always develop, and that behavioural and cognitive deficits were not ubiquitous [14, 15]. Thus, the clinical picture in affected adults differed from that in children presenting with the disorder, and in such patients, the need for surgical treatment was far less compelling.

The time was ripe for a meeting of many of the groups working in this area and this led to an International Symposium held at the Montreal Neurological Hospital in November of 2001*.

The embryological development and anatomy of the hypothalamus are thoroughly reviewed here, but the pathogenesis of the hamartoma remains uncertain. Not all hypothalamic hamartomas are epileptogenic, as shown by the number of patients with precocious puberty but no seizures. The distinctions between these two types of manifestations probably relate to the position and connections of the hamartoma. Pedunculated hamartomas below the third ventricle are rarely associated with seizures but may be associated with precocious puberty, whereas lesions within the third ventricle are often associated with seizures although precocious puberty is a variable feature (Freeman et al., this volume). Like malformations of cortical development elsewhere, hamartomas in this location are capable of epileptogenesis. The striking clinical symptomatology in children should indicate to the clinician the hypothalamic localization of the lesions, but the manifestations are varied, and a high index of suspicion must be maintained to avoid overlooking certain cases, particularly in adults (see Arzimanoglou *et al.* and Mullatti *et al.*, this volume).

Careful neurophysiological evaluation has done much to unravel the genesis of epilepsy (Kahane *et al.*, this volume). The idea that symptomatic generalized epilepsy and slow spike-waves may be generated by accessing thalamo-cotical loops via the mammillothalamic tract [8, 9, 12] received support from the data of Harvey and colleagues, who further developed the idea that this was a form of secondary epileptogenesis (16 and Harvey *et al.*, this volume). Functional imaging with PET reveals relatively widespread deficits, presumably reflecting the complex physiological disturbance set up the lesions (see Ryvlin, this volume).

Psychological and psychiatric complications of hypothalamic hamartoma have also come under scrutiny, and represent some of the major disabilities associated with these lesions and the epilepsy. Formal study of these is just beginning ([17], see Savard, this volume).

Hypothalamic hamartome can be associated with a number of genetic disorders, of which Pallister-Hall syndrome is the most important. It is noteworthy that seizures may be absent or relatively benign in most patients with this disorder (see Biesecker, this volume).

The different surgical approaches have developed according to the orientations and initiatives of the different groups. Systematic endocrine studies by the Melbourne group (see Freeman *et al.*, this volume) provide a solid foundation, and above all a baseline for our understanding of the complications of functional neurosurgery. A lateral pterional approach has advantages in the resection of lesions which extend laterally from the midline, but has the disadvantage of inaccessibility to lesions within the lumen or walls of the third ventricle ([18], Palmini *et al.*, this volume). The Melbourne approach of transcallosal resection has been the most successful to date. It appears to be the approach of choice for most cases, particularly for those patients with intra third ventricle extensions or lesions, which is typical of those lesions associated with seizures ([16, 19], see Harvey *et al.*, this volume). Disconnective surgery has its own advantages and appears to have a low rate of complications ([20], see Fohlen *et al.*, this volume). Stereotactic endoscopic and radiosurgical treatment seems effective (see Kuzniecky *et al.*, this volume), and gamma knife surgery appears to be a promising option, which still requires confirmation of its results by longer follow-up [21].

Apart from the preferences of individual surgeons and treatment centres, accumulated experience is leading to a confirmation of the approaches with the most effective seizure control with the least risk of vascular or other complications depending on the precise anatomy of individual lesions (see Polkey, this volume).

Most of the participants at the symposium intuitively considered that the completeness of the resection or disconnection correlated with the best outcome of surgery, and outcome data tend to support this. However, according to studies by Harvey's group, there is the suggestion that well-entrenched, secondary, generalized epilepsy may be a risk factor for poor surgical outcome, raising the issue of early surgery ([16], Harvey, this volume).

There are still many questions, particularly concerning patients with less than catastrophic epilepsy but whose seizures are nevertheless intractable. Are surgical approaches to these lesions justifiable, considering the risks? This remains an important question for the future.

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