

Hot-Water Epilepsy and Hyperthermic Kindling- Bridging Laboratory and Clinic

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Hot water epilepsy (HWE) is a type of reflex epilepsy triggered by a sensory stimulus specifically being a hot water bath, immersion in hot water or hot water shower [1].

Sensory epilepsy or reflex seizures induced by sensory stimuli are not uncommon phenomena [2]. In fact, Penfield first described it as long back as in 1941 [3].

Hyperthermia-induced seizures particularly precipitated by exposing the head to hot water are the second most common type of reflex epilepsy [4]. Hot water epilepsy was first reported in the year 1945 in New Zealand [5]. Thereafter, most of the cases have been reported from Southern parts of India for reasons not clearly defined [6-9]. Although, reports have come from the rest of the world as well [5, 9,10].

The pathogenesis of this type of reflex epilepsy has remained an enigma for several decades. However, we have made significant in-roads into it in the past few years [9-13] characterizing its genotype [11-13] and clinical phenotype [6,14] in the human populations. Large cohorts of patients with HWE attending their Tertiary Care Center of National Institute of Mental Health and Neurosciences (NIMHANS) in India were studied for over 4 years [6]. The study also investigated into other phenotypic variables of HWE such as gender (male>female), age (more common among young adults and children) and family history [14].

Thus, although in the past, HWE was being treated with some degree of skepticism in the clinical and scientific community, it has now been upgraded by being recognized as a reflex seizure precipitated by sensory stimulus by the International League against Epilepsy [15].

Electroencephalographic [14,16], pathological [17] and imaging studies [18,19] on patients with HWE by these groups of investigators further points out to a temporal lobe phenomenon in a vast majority although other cortical areas are not spared.

The high prevalence of HWE in the South Indian population has led to the possibility of a founder effect. This has been investigated and certain linkages with genes been indicated [12,13].

About 16-18% of the patients with HWE subsequently develop spontaneous seizures in the absence of a hot water bath [14]. Therefore, a timely intervention and prevention of these seizures becomes imperative. We found that early prophylactic treatment with oral benzodiazepines prior to taking the hot water bath successfully prevents the occurrence of these seizures [20]. Many other investigators have also confirmed the therapeutic effectiveness of clobazam [21].

My collaborators also found that although some families of probands with HWE have febrile seizures, another variety of hyperthermic seizures that is induced by fever [14] the genetic loci for these two seizure phenomena seem to be different [22].

Furthermore, in order to tie the loose ends of this epilepsy phenomenon together, we investigated it more extensively by developing an animal model for HWE [23,24]. Most importantly, through these models we confirmed that HWE is associated with a kindling phenomenon [25]. This “*Hyperthermic kindling*” is accompanied by seizures that are behaviorally as well as electrophysiological progressive [26]. Some of these animals even developed spontaneous

epileptic seizures [26]. There was robust mossy-fiber sprouting in the hippocampus in our animals with HWE [27,28].

Further, using differential-display reverse transcriptase polymerase chain reaction and sequence analysis and fold prediction strategies we discovered that in our rats with HWE there was an increased expression of mRNA that transcribes the brain development-related protein Bdm1 [29]. This protein is also implicated in homocysteine regulation pathway [29]. It is well known that homocysteine in turn increases glutamate binding to NMDA (N-methyl-D-aspartate) receptors of cortical and hippocampus [30].

Thus, not only does this saga of ours on hot water epilepsy, bridge the clinics to the laboratory but it also offers many tangible explanations and therapeutic approaches for neuroscientists and neurologists dealing with epilepsy.

Acknowledgement

Most of the reported work in this editorial was done in collaboration with Dr. Satish Chandra P, and Dr. Shankar SK of National Institute of Mental Health and Neurosciences; Dr. Panicker MM, Dr. Lakshminarasimhan N and Dr. Sowdhamini R of National Centre for Biological Sciences, Dr. Dadlani R, Dr. Kalladka, Dr. Rajashekhar, Dr. Krishnamoorthy and Dr. Archana of Ramaiah Medical College, Bangalore, India.

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Received May 05, 2016; Accepted May 15, 2016; Published May 18, 2016

Citation: Ullal G (2016) Hot-Water Epilepsy and Hyperthermic Kindling- Bridging Laboratory and Clinic. *J Depress Anxiety* S2: e001. doi: 10.4172/2167-1044.S2-e001

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