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Young boy with Addison's disease

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A 16 year old boy was admitted to the emergency department with two episodes of focal seizures. Each seizure was lasted for 2 to 3 minutes and occurred within 2 hours. He is being followed up at the endocrinology department for Addison's disease since the age of 11 years. This diagnosis was made when he presented with hyperpigmentation and dizzy episodes; confirmed biochemically with low basal and post synacthen cortisol with high Adreno cortico trophic hormone (ACTH) levels. Since then he was on hydrocortisone and fludrocortisone replacement. At the age of 14 years, he developed behavioural problems and also complained of suicidal thoughts. He was initiated on anti-depressants by the psychiatrist and his symptoms were settled. A year later he complained of occasional double vision and was investigated by the Neurologist. His physical examination and investigations including contrast tomography (CT) brain were normal. He was asymptomatic for the last 2 years until 4 weeks ago, where he developed mild difficulties in walking and mother noticed visual disturbances.

Physical examination revealed bilateral spastic legs with bilateral pale optic discs. His vital signs were normal.

What are the differential diagnoses?

- Untreated Addison's disease can present with neuropsychiatric symptoms. Mood disturbances, lack of motivation, behavioural issues and rarely psychosis and cognitive changes has been reported as presenting features. The possible mechanisms for this includes steroid deficiency, high endorphin levels, electrolytes and metabolic abnormalities [(1)].

- Associated other endocrine disorders such as Hashimoto's thyroiditis can present as Hashimoto encephalopathy. Majority are hypothyroid, but may be euthyroid or hyperthyroid. They may present with seizures, stroke like signs, psychosis, and cognitive impairment [(1)].

- Adrenoleucodystrophy, a rare genetic disorder should be considered in male child with Addison's disease.

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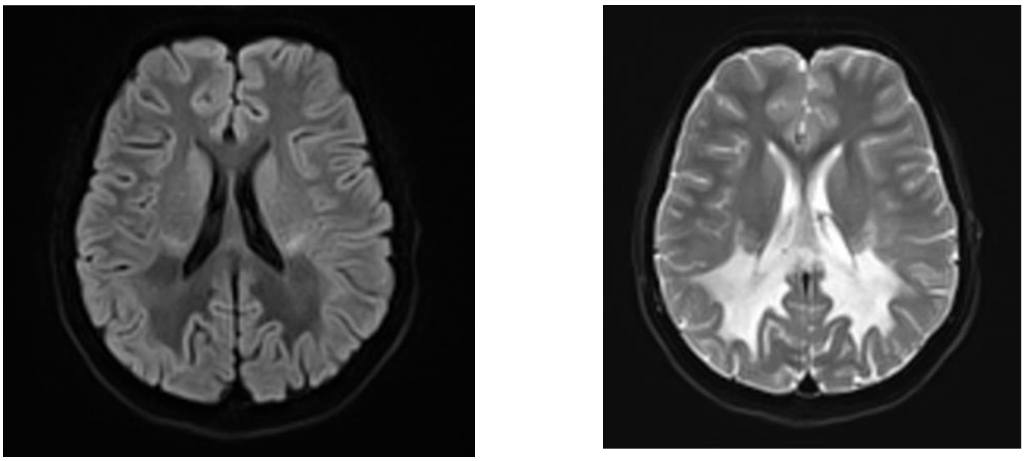

Figure 1: MRI brain of a boy with Addison's disease

What are the further investigations need to perform?

All routine biochemistry including electrolytes, cortisol day curve and thyroid function were normal. Figure 1 shows Magnetic Resonance Imaging (MRI) brain.

What are the radiological findings?

There is diffuse symmetrical T2 hyper-intensities involving both parieto occipital lobes and splenium of the corpus collosum. T1 imaging, there is central hypo-intense inter medial and peripheral zone. Post contrast imaging shows typical enhancement in inter medial zone represent active demyelination.

What is the clinical diagnosis?

Cerebral Adrenoleucodystrophy (ALD)

What is the prognosis?

ALD is a deadly X linked genetic disease. This disorder is caused by mutations in the *ABCD1* gene, which lead to high levels of very long-chain fatty acids (VLCFA) in the plasma that accumulate in the white matter of the brain, spinal cord, and adrenal cortex. This triggers an inflammatory response leading to demyelination[2]. There are different forms of ALD; the childhood cerebral ALD is the most devastating type. This form generally occurs between the ages of four and ten years old. The symptoms will start suddenly in an apparently normal child. At the onset they may have mild behavioural issues; poor attention, withdrawal, vision problems or mild issues with coordination. Gradually, the symptoms get worse as the disease spreads throughout the brain. They develop blindness, deafness, seizures, loss of muscle control, and progressive dementia. Ultimately this relentless downward spiral leads to a vegetative state or death, usually within 2-5 years of diagnosis [2].

What are the available therapeutic options?

- Hematopoietic stem cell transplantation (HSCT) remains the only disease-modifying therapy for ALD, with significant morbidity and mortality [3].

- Gene therapy trials with autologous hematopoietic stem cell transplant have shown short-term central nervous system disease stabilization in ALD without the morbidity and mortality of HSCT[3]

- Lorenzo's Oil - This is still considered experimental and may have some benefit in normalizing the

VLCFA, which may prevent the childhood cerebral form of ALD. This is not helpful for boys that are symptomatic[2].

- TRβ (Thyroid hormone receptor β) selective thyromimetics - In brain, TRβ has been proposed to play a role in the remyelination processes. Recently much effort has been applied in developing thyroid hormone analogs capable of beneficial action on central nervous system oligodendrocyte proliferation. Sobetirome and Eprotirome are the examples of TRβ selective thyromimetics [4].

What are the management options when the child was diagnosed too late for transplant?

If a child is not eligible or too late for transplant, providing multidisciplinary care is essential. There are variety of therapies available including physiotherapy as a supportive treatment to help muscle stiffness, build muscle strength, improve core stability, and relieve pain and recommending assistive devices. The aim is to provide the best quality of life possible.

What are the recent advances in ALD?

New-born screening for ALD has been started in some developed countries, which helps to identify pre-symptomatic children and allows early treatment[3].

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