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Case Report

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Update on Muscle Channelopathy

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1. Abstract

Skeletal muscle channelopathy are rare heterogeneous episodic disorders with marked genotypic and phenotypic variability resulting in periodic paralysis, and falls in young people which often misdiagnosed or undiagnosed due to its rarity, often the symptoms are miscommunicated to the treating phycision due to its episodic nature and not uncommonly physical examination by the time patient attend the clinic or hospital will be unremarkable apart from periodic muscle paralysis where patient will presented to ED with flaccid weakness,

In this review we will present two patients where the diagnosis was initially missed, and it took some time to reach the correct diagnosis.

2. Case Report

2.1. Case 1

23-year patient presented with difficulty of breathing after he finished a soccer match, in addition to back pain, he was transferred to the nearest hospital, clinical examination was unremarkable, ECG was sinus rhythm, no ECG changes of ischemia or repolarization ray was normal chest [1], Oxygen saturation was 100% on room air, arterial blood gases was normal, the following blood tests were either normal or negative, Full Blood Count, Liver function tests, Kidney function, metabolic panel, ESR, CRP, Iron study, B12, Folate, Methyl Malonic acid, haemocystein, exhaled nitric oxide, Lung function test including challenge with methacholine to exclude Bronchial Asthma and hypersensitive air ways, Patient was diagnosed as hyperventilation and discharged home [2], patient represented next day with difficulty to drink cold tea and chest tightness after 30 minutes training in the Gym, Patient readmitted to the hospital for more investigation [3], basic investigation in addition to cardiac troponin , brain nature tic peptide(PNB), thyroid function tests transthoracic echo, uncontracted CT head were done and all came normal, normal ,neurology senior registrar was consulted to see the patient ,detailed neurological examination was unremarkable [4], examination of the fundus after pupillary dilation showed no abnormality, barium swallow ruled out any anatomical abnormality, patient was booked for esophageal motility study [5] ,and arranged to be seen in outpatient clinic, Two days later patient was admitted to the hospital with chest tightness, back pain, and unable to swallow cold orange juice [6], patient admitted to the hospital for further work up, Basic blood tests were repeated, Pan MRI was ordered, esophageal motility study was done in his recent admission, all investigation came either negative or normal apart from CK which was 1000 U/L (10-80 u/l), speech service was consulted to assess swallowing which ruled out any esophageal or non-esophageal dysphagia, repeated CK came normal next day, the initial high CK was explained as a Lab error [7], patient was reassured and advised to be seen by a psychiatrist for functional disorder [8,9], Patient was seen by a psychiatrist next day for assessment of patient mental health, Psychiatrist concluded that a through interview with the patient was done and he did not support the diagnosis of functional disorder and advised that patient [10,11] discharged from his clinic and should be seen by a multidisciplinary team should he developed any further symptoms, Patient readmitted to the hospital one week later as he could not catch his breath and not able to move his left side of his jaw, urgent MRI stroke protocol was done and did not

reveal any restriction defect, MRI with Gadolinium did not show any enhancement, CK came 900u/l (10-80), A medical student was asked to take a detailed history from the patient as well as a detailed neurological and systemic examination, Patient gave a history that his brother had similar symptoms before affecting mainly his legs, Medical student that patient after exercise found difficulty to relax his face [12], and repeated CK is 1110U/I, Patient was taken to the electrophysiology lab where nerve conduction study was normal but EMG diagnosed electrical myotonia of the jaw and thoracic muscles [13], patient started on oral Acetazolamide, and counselled for genetic testing which came positive for SCN4A confirming the diagnosis of Para myotonia Congentia.

2.2. Case 2

22-year-old patient presented with palpitation and shortness of breath, seen in ED where cardiac examination showed bradycardia of 50/min with no drop in blood pressure, JVP was not elevated, Rest of cardiac examination was normal, ECG did not show any ischemic changes, prolonged Holter monitor for 4 days did not show any arrythmias, cardiac enzymes and BNP were normal, thyroid function test, electrolytes, iron study, B12, folate were normal, chest X ray and transthoracic echo cardiogram did not show any abnormalities, patient reassured and sent home, Two weeks later patient was readmitted with palpitation and weakness of both legs [14], Examination revealed weakness in both hip flexors 3/5 with normal sensation [15,16], diminished knee reflexes and dawn going planters showed polymorphic extra systole and marginally prolonged Q-T of 480ms (360-460ms), the following blood test were normal or negative, FBC, LFT, U, E, Metabolic panel Thyroid function test, cardiac troponin, BNP, Vasculitis panel, autoimmune panel, septic screen [17], Acetyl choline receptor antibodies, Anti MUSK antibody, RI for whole spine was normal, CSF was non-reactive, transthoracic Echocardiogram was normal [18], next day patient improved spontaneously, Patient was sent home and outpatient appointment was arranged for exercise test, During exercise test patient had to stop in stage 1 because of weakness in both legs and ventricular tachycardia [19,20], exercise was stopped, patient given 2 mg IV metoprolol and admitted to ICU for observation, patient was Asymptomatic in ICU, after 24 hours observation , patient moved to medical ward for more work up [21], detailed examination showed patient had dysmorphic features which encompass short stature, low set ears,microgantheia, short palpebral fissures, short nose with fullness along the bridge, Broad forehead, high arched palate, Bulbous tip of the nose, cleft palate, triangular face, Syndactyl of the 2nd and 3rd toes, Digit clinodactyly, cognitive assessment showed deficits in executive functions and abstract reasoning, patient deemed unable to make decisions, family was invited for a meeting to discuss future management , it was decided that patient will benefit from implantable cardiac defibrillator [22], and genetic testing to exclude Andersen – Tawil Syndrome, Genetic sequencing confirmed positivity for KCNJ2, also patient started on acetazolamide, Other members of the family offered genetic testing but declined [23].

3. Discussion

Skeletal muscle Channelopathy are a family of rare genetic neuromuscular disorders causing impaired muscular contraction [24], relaxation or both caused by dysfunction of sarco- lemmal ion channels that is essential for muscular membrane excitability caused by a mutation in Voltage – gated sodium [25], Potassium, Chloride and calcium channels, the diagnosis is often delayed as symptoms are episodic and usually difficult to be described by patients, although symptoms are benign but it can cause disability ,embarrassment of the patients, social isolation and rarely can cause death [26] if it affected the larynx causing laryngospasm and cyanosis and loss of consciousness and commonly interpreted as a seizure, Membrane depolarization hyper excitability can cause myotonia and hypo excitability can cause weakness and paralysis [27], channelopathy encompassed periodic paralysis and non-dystrophic myotonia, Periodic paralysis encompasses hypokalemic periodic paralysis, hypokalemic periodic paralysis and Andersen – Tawil Syndrome [28], Non dystrophic Myotonia could be Myotonia Congenita or para myotonia congenital.

3.1. Periodic Paralysis

Periodic hypokalemic, hypokalemic and Andresen – Tawil syndrome (ATS) are all autosomal dominant disorders, Hyperkalemic periodic paralysis are caused my mutation in the Sodium channel gene SCN4A , Hypokalemic periodic paralysis is caused by mutation in Calcium Channel gene CACNA1S on chromosome IQ31, Andresen -Tawil Syndrome is caused by mutation in the potassium channel, Gene KCNJ2 on chromosome 17Q23, severity of weakness can vary from mild to severe, during weakness jerks are diminished, sensation will be intact, skeletal muscles are only affected, straited muscles (Bowel and bladder) are not affected, over time patient will develop irreversible proximal myopathy, patient also can suffer from fatigue and myalgia, hypokalemia can induce ECG changes in the form of inverted T, depressed ST Segment and U wave, which are indication of intravenous potassium, 40 ml KCL in 1 liter saline with rate of 10ml/hour, examination between attack's is usually normal, Patient with hyperkalemia might develop myotonia, weakness might last minutes to hours, triggered by high potassium food and cold drinks, patient might be able to walk on even ground but can't climb stairs, sometime weakness might be task specific like weighting with one arm or kicking the ball one one leg, also weakness specific to rest after exercise, potassium sparing diuretics can trigger weakness, Hypokalemic periodic Paralysis is the most common skeletal channelopathy, although respiratory and cardiac muscles are not affected, life threatening arrythmia and respiratory failure had been reported, Mutant channels induce an inward cation leakage current which decreased the threshold of muscle fibers to aberrant depolarization in response to increase intracellular potassium and decrease extracellular po-

tassium, that is why this patient should be monitored after normalization of the serum potassium to make sure that they did not develop rebound hyperkalemia due to movement of intracellular potassium to the extracellular compartment, patient with periodic hypokalemia should have a work up to exclude renal tubular acidosis, gateman syndrome, hyperaldosteronism, Cushing syndrome, potassium losing diuretics, thiazide and frusemide intake , vasoactive intestinal peptide VIPoma, diarrhea and vomiting, salt losing Nephropathy , Fanconi syndrome, Thyrotoxicosis 85 % of patients with hypokalemia will be autosomal dominant and CACNA1 mutant, rest is autosomal recessive with SCN4A mutation, Rest is autosomal recessive and SCN4A mutant, Korean J Pediatr had recently identified alter subcellular distribution of a calcium – activated potassium channel in skeletal muscle cells of patients with hypokalemic periodic paralysis

3.2. Andresen -Tawil Syndrome

It a multisystem disorder characterized by dysmorphic features, cardiac arrythmia due to conduction defects, prolonged Q-T ,episodic paralysis in the first or second decade of life, commonly associated with hypokalemia, and uncommonly hyperkalemia, precipitating factors are similar to hypo and hyperkalemia, fixed proximal myopathy usually occurs, myotonia usually does not occur, sudden cardiac death had been reported , most patients will need antiarrhythmic medications , up to 15% of patients will need implantable cardiac deliberator, expert opinions recommend patient should have annular review by an expert electro physiology cardiologist and prolonged Holter monitor , despite prolonged Corrected Q-T interval is the most common abnormalities, U wave amplitude is the most sensitive ECG Abnormality to differentiate ATS from polymorphic ventricular tachycardia, muscle biopsy frequently shows tubular aggregates and nonspecific myopathic changes

3.3. Non-Dystrophic myotonia

Majority of patients with non-dystrophic myotonia have primary or secondary loss of membrane chloride conductance due to reduction in the resting membrane potential, Non dystrophic myotonia are now known to be caused by dysfunction of skeletal muscle ion channels Which include myotonia congenitia, par amyotonia congenitia and sodium channel myotonia, Common symptoms are delayed relaxation of muscles following muscles contraction, or exercise, EMG showed repetitive muscles fiber after discharge, Myotonia Congenital is caused by a mutation in the skeletal muscle Chloride channel gene either autosomal dominant or recessive,(CLCN-1),legs usually affected more than face and arm and this explained the frequent falls in Myotonia Congenita(MC), symptoms triggered by prolonged rest after exercise, and change in temperature, warm enviroment can alleviate myotonia, warm up phenomena is characteristic of myotonia (exercise after developing myotonia will abort it), weakness is usually brief and disappear with exercise, patient usually develop hypertrophy of calf muscles,

3.4. Par amyotonia Congenita

It is characterized by marked sensitivity to cold, face and hands are affected more than legs, warm enviroment relived myotonia, patients would not help by exercise I.E negative warm up phenomena, in fact, patients with par amyotonia will get worse with exercise with develop paradoxical myotonia which is characteristic for para myotonia, patients usually develop a prolonged time of weakness, Not uncommonly misdiagnosed as hyperkalemic periodic paralysis, muscle hypertrophy can be generalized, usually it is autosomal dominant and SCN4A mutated.

3.5. Malignant hyperthermia

Malignant hyperthermia is a serious channelopathy where the mutation RYR1 causes hypersensitive channels causes efflux of calcium from sarcoplasmic stores to myoplasm causing muscle rigidity and hyperthermia in response to volatile anesthetics and depolarizing muscle relaxants, this causes depletion of ATP and upregulates glycogenolysis causing metabolic acidosis, increased oxygen consumption and carbon dioxide production leading to sever hypoxia, hypercapnia and rhabdomylosis, hyperkalemia and multiorgan failure.

3.6. Diagnosis and differential diagnosis

Diagnosis depends mainly on history and normal examination in between attacks and confirmation with genetic study, because the disease is very rare and patient find difficulty to describe the symptoms, usually the diagnosis is delayed, clinicians should concentrate on the history rather than on the examination, family history is extremely important as most of the channelopathy are autosomal dominant apart from Myotonia congenita which could be autosomal dominant or recessive, EMG plays important role in confirming electrical myotonia, Important hints in the history are, when was the first-time patient had the symptoms, which part of the body affected first, legs or limb and face, what triggered the symptoms, is it rest after exercise, or lower body temperature, medication whether potassium sparing or potassium depleting diuretics.

How long for was the weakness, did exercise help the weakness or made it worse (Warm up phenomena or paradoxical myotonia in par amyotonia congenita), did patient have pain and fatigue, were the bladder or bowel involved (usually no as they are not skeletal muscles), did patient lose alertness or consciousness (usually no otherwise seizure will be the differential diagnosis specially if all attacks are stereotyped) , if patient can walk on flat even ground but can't not climb stairs, does patient have proximal myopathy from long standing recurring attacks ,ictal potassium and CK is important clue to the diagnosis ,patient with myotonia congenita can be diagnosed from the waiting room as they when they arise after waiting seated , their might have difficulty because of myotonia and stiffness and once they reach the room , they be-

come normal, examination might show myotonic eye lid or hand grip, Patient with paramyotenia congentia will develop paradoxical myotonia after exercise, Patients with Andersen -Tawil syndrome will have dysmorphic features and usually they have cardiac symptoms from conduction blocks, occasionally they have myotonia but classic symptoms are hypokalemic periodic paralysis, Differential diagnosis including but not limited to pomp's disease which is a glycogen storage disease cauterized by muscle weakness, organomegaly, in adult form of the disease, patient will have hyperkaliemia, Episodic ataxia are a group of genetic disease chacterised by paroxysmal truncal ataxia and incoordination which usually last from minutes to hours, most have an autosomal dominant pattern, diagnosis can be confirmed by genetic study for KCNA1 and CACNA1A mutation

3.7. Treatment

Skeletal muscle channelopathy are incurable but symptoms can be ameliorated by removing triggering factors like exercise or rest after exercise which trigger myotonia, it is important to find a balance of exercise which could not provoke symptoms, patient with paramyotonia congentia may require rest period after balanced exercise, patients with myotonia avoid sudden movement and instead increase severity of exercise very gradually, patients should avoid cold weather by appropriate clothing. Medications which help symptoms are mainly Sodium channel blockers, mainly Mexiletine which is first line for non-dystrophic myotonia, Lamotrigine which is anticonvulsant and voltage gated sodium channel blocker whose mode of action is slow binding to the fast inactivated voltage gated sodium channel and shifting of the voltage gated dependance of inactivation to more negative potentials.

3.8. Carbamazepine

A well stablished anticonvulsant for decades and showing promising effects on many studies.

3.9. Flecainide

Class 1c antiarrhythmic, contra indicated in patients who had structural heart disease.

3.10. Ranolazine

Mode of action enhances slow inactivation of voltage gated sodium channels and blocks persistent Voltage dependent sodium inward current.

3.11. Acetazolamide

It is a carbonic anhydrase inhibitor and can prevent periodic paralysis, it is useful for patients with periodic paralysis and myotonia in the same time like hyperkalemic periodic paralysis, Side effect included renal calculi and renal tubular acidosis.

4. Summary and Conclusion

Patients with skeletal muscle channelopathy will have common symptoms of a rare daises, Diagnosis is mainly on the history including detailed family history and not on the examination, All common investigation for skeletal muscle channelopathy is negative or normal [29], Hypokalemia with normal acid balance is a hint that patient might have genetic hypokalemic periodic paralysis, Secondary causes for hypo or hyperkalemia should be ruled out including and not limiting to potassium losing diuretics, primary hyperaldosteronism, paraneoplastic Cushing syndrome, distal renal tubular acidosis , Fanconi syndrome, use of laxative, salt losing nephropathy, use of corticosteroids, syndrome of inappropriate ADH,Gittelman syndrome, potassium rich food , potassium sparing diretics,adrenal insufficiency,

Episodic movement disorder can be confused with skeletal muscle channelopathy, Patients with skeletal muscle channelopathy could be manifested by intermittent fatigue syndrome [30], Dysmorphic features should not be ignored as it is one of the manifestations of Andersen- Tawil Syndrome, although routine blood tests are normal in skeletal muscle channelopathy, genetic testing is fundamental to diagnose and confirm the disease

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