BRUTON'S AGAMMAGLOBULINAEMIA IN A CHILD PRESENTING WITH CRYPTOCOCCAL EMPYEMA THORACIS AND PERIAURICULAR PYOGENIC ABSCESS

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ABSTRACT

We describe here a case of cryptococcal empyema thoracis and periauricular pyogenic abscess in a child with Bruton's agammaglobulinaemia. The cryptococcal empyema thoracis was treated with intravenous amphotericin B and intravenous fluconazole for six weeks followed by oral fluconazole. The pyogenic periauricular abscess was surgically drained and treated with intravenous ceftazidime and cloxacillin for two weeks. He also received monthly intravenous immunoglobulin.

Keywords: *amphotericin, Bruton's agammaglobulinaemia, cryptococcal empyema.*

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INTRODUCTION

In 1952 Bruton described a male child with hypogammaglobulinaemia. Subsequently many other names were given to this disease - including "congenital", "infantile", sex-linked agammaglobulinaemia, as well as "panhypogammaglobulinaemia"[1]. We describe a child who presented with a history of recurrent pyogenic bilateral ear infections, multiple skin abscesses and episodes of unilateral empyema thoracis since infancy. He had low serum immunoglobulins of all classes and a total absence of the B-cell population. However, peculiar to him was the unilateral cryptococcal empyema thoracis despite the normal population of T-cells and phagocytes (neutrophils).

CASE REPORT

A five-year-old Malay boy presented to the Ear, Nose and Throat Department for swelling, redness and pain of the right periauricular region of one month's duration. His problem started off with pussy discharge from both ears. During the one-month period, he also had frequent episodes of productive cough (yellowish sputum) associated with increasing shortness of breath, high grade fever with chills and rigors. His appetite and weight were markedly reduced. There were no chest pain, haemoptysis and cyanosis or any history of headache, fits, joint pain, abnormal bowel or urinary habits. Since the age of one year old he had had frequent episodes of bilateral ear infections which were treated in the government hospitals and by several general practitioners. Prior to this, the child had been admitted twice for unilateral empyema thoracis. He had also developed frequent episodes of skin abscesses which either resolved spontaneously or required treatment.

He was delivered normally at home by a trained midwife. The delivery was uneventful and he was well until about one year of age. He is the only child among five children suffering the illness. His parents were of non-consanguineous marriage. He has a younger brother who was three years old and three sisters whose ages were three months, nine years and twelve years. There was no similar illness in the family. There was no history of rearing birds or frequent contact with birds. He came from a very poor socioeconomic background. His father worked as a television and radio repairer and earned about RM300.00 per month. His developmental milestones were normal. His immunisations were incomplete as he only received BCG, two doses of DPT and oral polio.

On examination he appeared cachexic, pale, tachypnoeic and febrile (39°C). However he was alert and conscious. His weight and height were 10.5 kg and 91 cm respectively. He was below the 3rd centile for weight and height, equivalent to those of a three-year-old boy. He was tachycardic with a pulse rate of 110/min and his blood pressure was 100/70 mmHg. The right periauricular region appeared swollen, inflamed and tender (Fig 1). The left pinna was retracted. Both ears discharged a foul smelling pus. His hair was coarse and light brown in colour and there were several superficial small abscesses noted above the left eyebrow. Both his pupils were reactive to light and his fundi were normal. His throat was inflamed but there were no tonsils seen and the lymph nodes were not palpable. His skin was scleremic with multiple brownish scars seen over both lower and upper limbs. A scar was seen over both the left chest wall: this was the site of a previous chest tube insertion.

His trachea was deviated to the right with reduced chest expansion on the left side. The chest was dull on percussion and bronchial breathing was heard over the left mid-zone. There were minimal crepitations heard over the left lower zone. His abdomen was soft and not distended, and the liver was about 3 cm below the right subcostal margin. Both the spleen and kidneys were not palpable and bowel sounds were heard.

On admission, his haemoglobin was 6 gm/dl (normal 13.5-17.5 gm/dl). The total white cell count was 10.8 x 10^9/l (normal 4.0-11.0 x 10^9/l) with polymorphs of 7.5 x 10^9/l (normal 2.5-7.5 x 10^9/l) and the rest were lymphocytes. The platelet count was 300 x 10^9/l (normal 150-400 x 10^9/l).

His chest X-ray showed consolidation of the left middle and lower zones with obliteration of the left costo-phrenic angle (Fig 2). Sputum for acid fast bacilli was negative and there was no reaction to the Mantoux test. ELISA test for HIV was also negative. The ear swabs grew mixed organisms (*Staphylococcus aureus* and *Pseudomonas spp*). Cryptococcal spp. was isolated

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Fig 1 - Child with Bruton's agammaglobulinaemia showing ear before treatment.

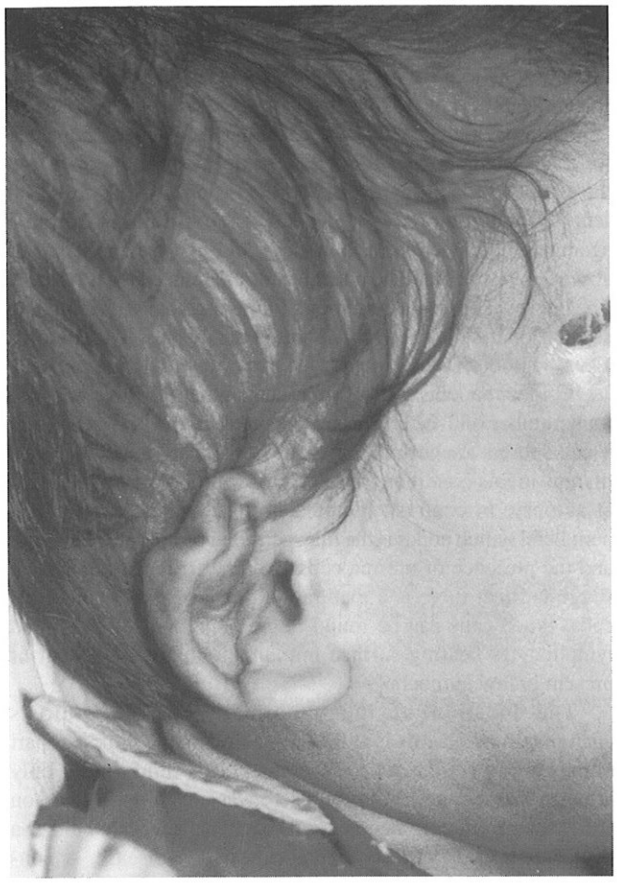


Fig 2 – Chest X-ray of the child with Bruton's agammaglobulinaemia taken on admission.

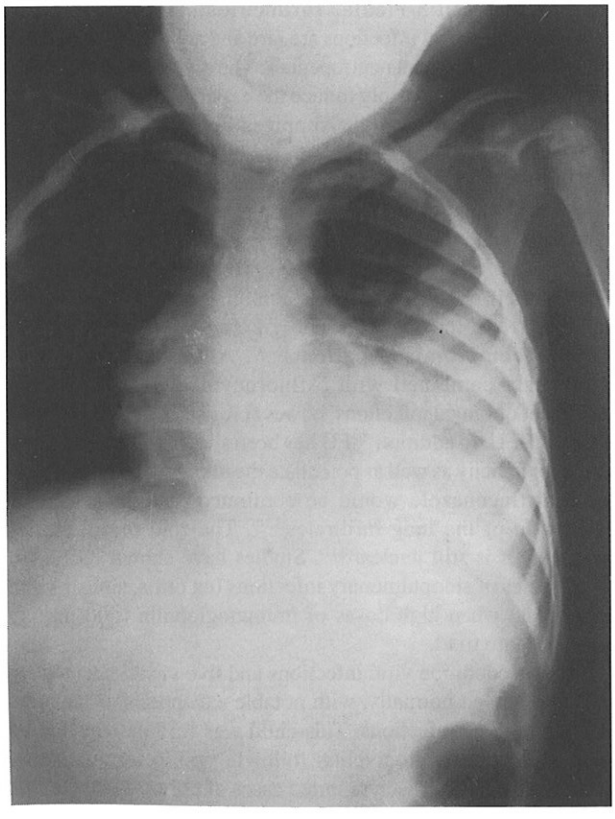


Fig 3 - Child with Bruton's agammaglobulinaemia showing ear after treatment.

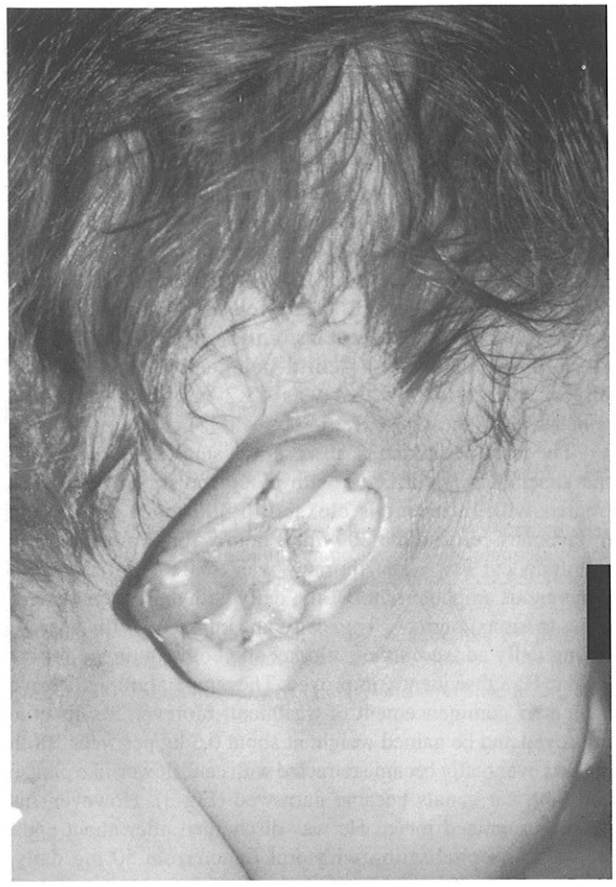
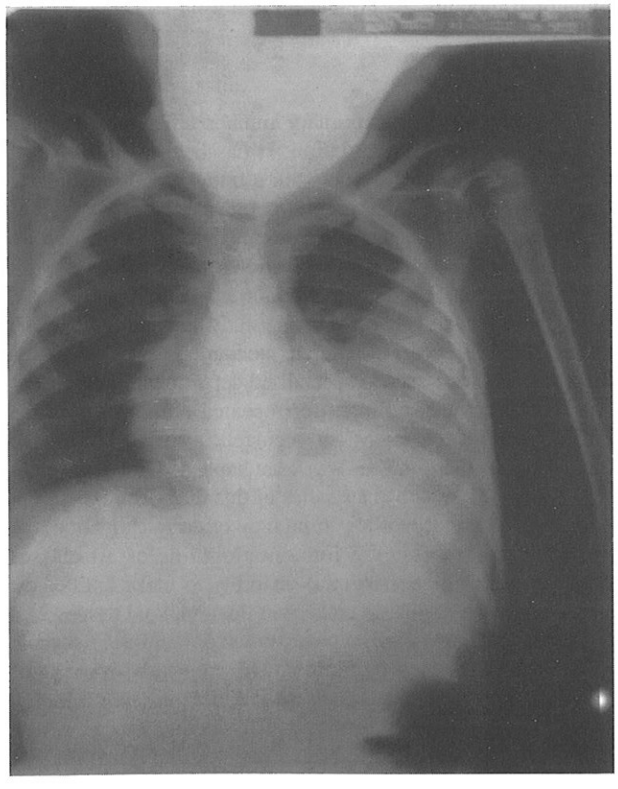


Fig 4 – Chest X-ray of the child with Bruton's agammaglobulinaemia taken at discharge showing minimal resolution of the cryptococcal empyema thoracis.



from the pleural fluid after a diagnostic tap and latex agglutination (antigen detection) for *cryptococcus* was also positive.

The nitroblue tetrazolium test was within normal limits with more than 20/100 neutrophils turned blue (normal > 10/100 neutrophils) and 27/100 neutrophils turned blue a month later. His serum immunoglobulin levels were all low with IgG< 2.50 g/l (normal = 5.5 - 14.0 g/l), IgA < 0.30 g/l (normal = 0.35 - 2.50 g/l) and IgM < 0.320 g/l (normal = 0.40 -1.50 g/l). He was rhesus A positive. Flow cytometric immunophenotyping results showed total T-cells of 3410 cells/mm^3 (normal 1800-3000 cell/mm^3), T helper/inducer of 1690 cells/mm^3 (normal 1000-1800 cells/mm^3), T-cytotoxic/suppressor of 1390 cells/mm^3 (normal 800-1500 cells/mm^3), complete absence of B-cells (normal 700-1300 cells/mm^3) and natural killer cells of 220 cells/mm^3 (normal 200-600 cells/mm^3). The lymphocyte transformation test was normal with stimulation index of the child being more than 10. The phytohaemagglutinin test was 43.2 (Control 43.2) and concanavalin A test was 27.1 (Control 15.6).

The right periauricular abscess was surgically drained and the anaemia was corrected with blood transfusions. He was treated with intravenous cloxacillin 300 mg 6 hourly and intravenous ceftazidime 200 mg 8 hourly for two weeks. The cryptococcal empyema thoracis was treated, initially with intravenous amphotericin B 1 mg daily with daily increment of doses to a maximum of 10 mg daily, and intravenous fluconazole 35 mg daily added on the fifth day and both continued for six weeks. He subsequently improved. The temperature settled five days after commencement of treatment. Morever, his appetite improved and he gained weight at about 0.5 kg per week. Both his ears eventually became retracted with cauliflower-like pinnae and both ear canals became narrowed (Fig 3). However, his hearing remained intact. He was discharged after about eight weeks of hospitalisation with oral fluconazole 50 mg daily. Repeated chest X-rays showed minimal resolution of the affected lung (Fig 4). Latex agglutination test for cryptococcal antigen at discharge was still positive. He is at present receiving monthly intravenous gammaglobulin of 2.5 gm (dosage 200mg/kg). His serum immunoglobulin levels were being monitored biweekly. Serum latex agglutination for cryptococcal antigen is also being monitored monthly. At present he is not on any prophylactic antibiotics.

DISCUSSION

The prevalence of known primary immunodeficiencies is about 1 child per 100,000 population. It has been estimated that agammaglobulinaemia occurs with a frequency of 1 child per 50,000 population[2]. At present, the prevalence in Malaysia is not known but we believe these cases are under reported. Studies in Japan and Great Britain have shown that 62% to 83% of primary immunodeficiencies in children occur in the male[3]. Often the diagnosis is late and in one study the time of diagnosis varied from 1 to 5 years in children (median 2.5 years)[4]. Usually, these patients were seen in specialised departments such as Ear, Nose and Throat department for repeated otitis media or the Orthopaedics department for recurrent arthritis before the diagnosis was made[4]. This was what happened in our case.

The identifying characteristics of this disease are recurrent pyogenic infections starting in infancy or early childhood, the virtual absence of serum immunoglobulins of all classes (panhypogammaglobulinaemia), inability to make antibodies, and the absence of plasma cells from the lymphoid tissues[2].

In this child, the clinical presentation of recurrent pyogenic ear infections, frequent multiple skin abscesses and episodes of unilateral empyema thoracis since the age of one year is highly suggestive of primary immunodeficiencies, among which common variable immunodeficiency (CVID), transient hypogammaglobulinaemia of infancy or chronic granulomatous disease (CGD) were the other possibilities besides Bruton's agammaglobulinaemia. Clinically, CVID was unlikely because the age of presentation is usually in the older age group, the infections are usually less severe and the child has normal-sized or enlarged tonsils and lymph nodes. The occurrence of splenomegaly is only found in about 25% of the cases. In transient hypogammaglobulinaemia of infancy, the patient usually appears well and the immunoglobulin concentrations become normal after the age of 18 months. Only in the rare instance would the child require treatment. Although CGD may simulate Bruton's agammaglobulinaemia, it is unlikely in this case as there was absence of tonsils and the nitroblue tetrazolium test was normal. The low level of serum immunoglobulins together with complete absence of B-cells strongly supported the diagnosis of Bruton's agammaglobulinaemia.

In most patients with Bruton's agammaglobulinaemia, the total number of T-cells is usually increased, the percentages of T-cell subsets are normal, and the T-cell function is intact. The thymus in this condition appears to be morphologically normal at autopsy. In contrast, hypoplasia of adenoids, tonsils, and peripheral lymph nodes is the rule; germinal centres are not found, and the presence of plasma cells are rare. Recent studies have suggested that there is a maturation arrest of pre-B cells to B cells. Pre-B cells can be found in the bone marrow but blood lymphocytes bearing surface immunoglobulins are absent or present in low numbers[3].

The location of the abnormal gene in Bruton's agammaglobulinaemia is at the q22 region on the proximal part of the long arm of the X-chromosome[2]. This child was the only affected member in the family. There was no similar disease on either the paternal or the maternal side. This suggested either a new mutation or variable expression of the disease. A non-familial occurrence has also been documented[5]. Family screening is essential to identify the carriers but this has been refused by the parents.

The most common type of infections known to complicate Bruton's agammaglobulinaemia include pyogenic sinusitis, pneumonia, otitis media, furunculosis, meningitis and septicaemia. Fungal infections are rare and are usually as a result of associated persistent neutropenia[2]. The cryptococcal infection in our child could possibly induce the expansion of a suppressor cell population that might suppress both the delayed-type hypersensitivity and the development of T-cells responsible for inhibiting the growth of the organisms[6].

Intravenous fluconazole was added to amphotericin B after five days since there was no improvement of the condition in this child. At present, it is generally recommended that amphotericin B given alone or in combination with fluconazole is the treatment of choice in fungal infections in immunocompromised patients[7,8]. Amphotericin B was previously combined with 5-fluorocytosine (5-FU) in the treatment of fungal infections, however resistance has developed against 5-FU. In addition 5-FU has been shown to cause marrow and liver toxicity as well as potentiate the toxicity of amphotericin B. Oral fluconazole would be continued in this child until resolution of the lung infiltrates[9,10]. The role of antibiotics prophylaxis is still unclear[2,11]. Studies have shown decreased frequencies of sinopulmonary infections (eg otitis, sinusitis and bronchitis) when high doses of immunoglobulin (600 mg/kg/month)[12] are tried.

In this condition viral infections and live virus vaccines are usually handled normally, with notable exceptions of hepatitis and enterovirus infections. This child was fortunate in that he did not develop poliomyelitis following polio immunisation although there have been reported cases of poliomyelitis in this

condition following polio immunisation[2]. The parents of this child had been advised not to give the child any hepatitis B immunisations.

Long-term follow-up of the child is essential since treatment with intravenous immunoglobulin[1-5,13,14] is life-long. Vigilance on the development of complications such as chronic lung disease, leukaemia, lymphoma, connective tissue diseases and the development of fatal persistent viral infections of the central nervous system particularly by *echovirus* is necessary during the follow-up. Although such patients may survive up to the second or third decades or beyond, their prognosis is still guarded[3].

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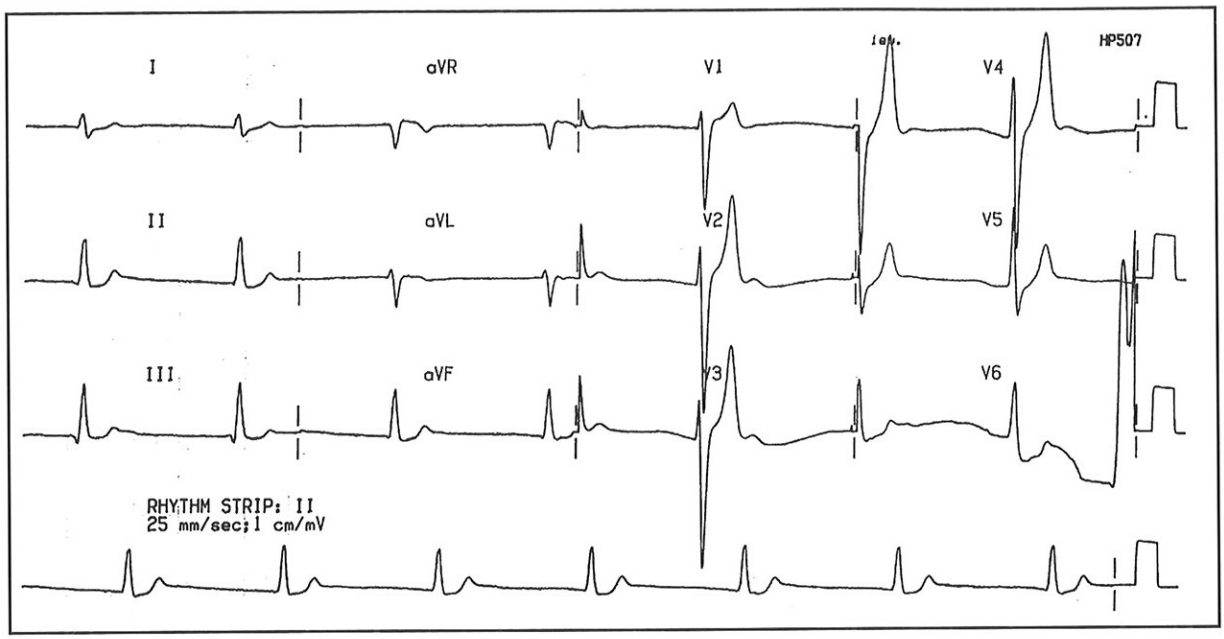
Fig 2 - 12-lead electrocardiogram after initial treatment with intravenous calcium chloride, sodium bicarbonate and dextrose/insulin.



ANSWER TO ELECTROCARDIOGRAPHIC CASE

Diagnosis: Severe hyperkalaemia from chronic renal failure with severe metabolic acidosis.

DISCUSSION

ECG (Fig 1) done before treatment, corresponding to a serum potassium level of 8.7mmol/l, shows very classical features of severe hyperkalaemia ie,

- Very peaked, symmetrical and tall T waves with a narrow base[1-7]. [Note: tall T waves are best seen in the precordial leads, especially V2-4[4-6]]
- Absent P waves[1-8] and irregular ventricular rhythm due to periods of ventricular asystole[4]
- Widened QRS complex to 0.26 sec[1-8]
- ST elevation in V1-4[5,7] (but uncommon)
- Merging of S wave into T wave, producing a wide bizarre, diphasic deflection[2,6]
- Diminution in the amplitude of R wave[2]
- Irregular junctional rhythm[7]
- Left axis deviation[7]
- Left bundle branch block[1]
  [Note: Transient bundle branch block can be seen in hyperkalaemia[9].]

Arterial blood gas done showed the following: pH 7.108, PCO_2 24.2, PO_2 106.3, BE - 19.6, SBC 10.6, O_2 saturation 95.9%. She was given 10% calcium chloride 10 ml at 0840 hours, followed by intravenous 4.2% sodium bicarbonate 20 ml, and then intravenous 50% dextrose 50 ml with 12 units soluble insulin.

Seven minutes after the above treatment, the repeat ECG is markedly different (Fig 2).

The most obvious difference is the narrowing of the QRS complex. The T waves are now slender, scooped, tented and tall as in classical hyperkalaemia. However, the P waves are still absent. The rhythm is junctional bradycardia with a ventricular rate of 38/min. The potassium level at this stage was 7.6 mmol/l.

A further intravenous 10% calcium chloride 10 ml and 4.2% sodium bicarbonate 20 ml were given.

The repeat ECG is shown in Fig. 3.

The P waves have reappeared, suggesting sinus rhythm and the heart rate is now 58/minute. At this stage the BP picked up to 127/50mmHg. The patient was then admitted to the intensive care unit where she was given further intravenous 50% dextrose 20 ml with 10 units soluble insulin. She was started on resonium A 15g tds and haemodialysis. She was discharged from hospital alive a week later.

TREATMENT OF HYPERKALAEMIA

Hyperkalaemia is a metabolic emergency. The 2 main systems of the body affected by hyperkalaemia are the skeletal muscle and cardiovascular system. However, it is the cardiovascular complications which is life-threatening as it may cause sudden death from asystole or ventricular fibrillation. It is interesting to note also that the ECG changes in hyperkalaemia are exaggerated by hypocalcaemia, hypermagnesemia, hyponatremia and acidosis[1].

Classification of hyperkalaemia[6]

The severity of hyperkalaemia depends on plasma potassium and the ECG.

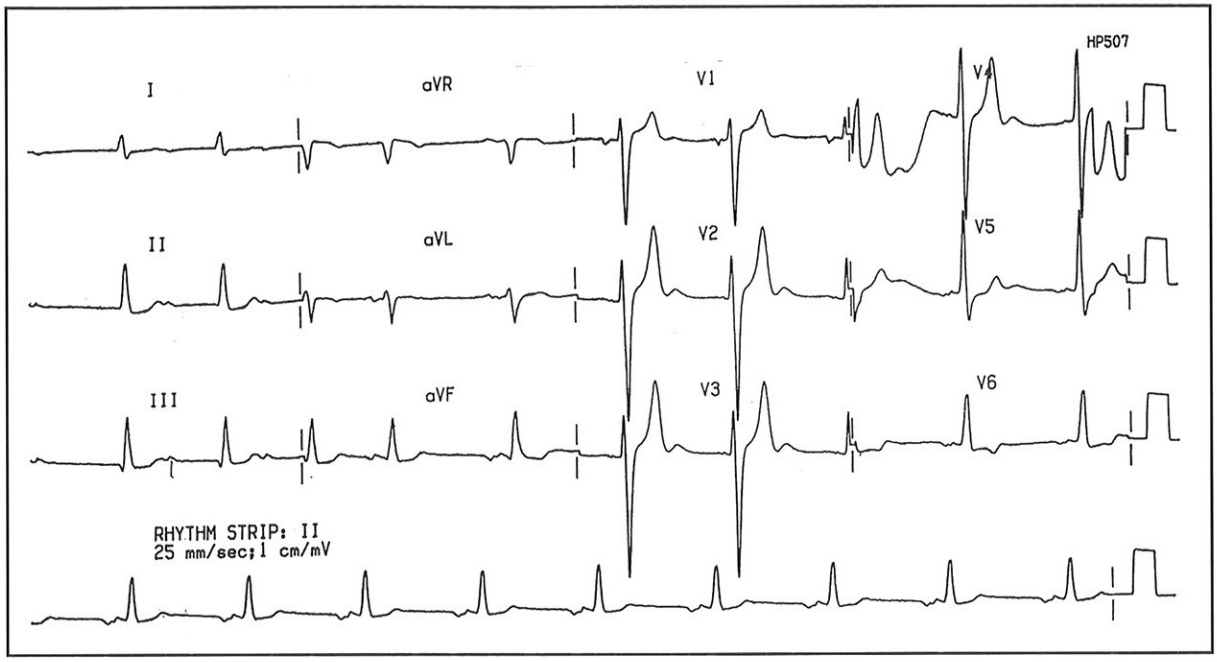
Mild	:	Potassium level < 6.5 mmol/l and ECG shows only peaked T waves.
Moderate	:	Potassium level 6.5-8.0 mmol/l and ECG shows peaked T waves.
Severe	:	Potassium level > 8.0 mmol/l or ECG includes absent P waves, widened QRS or ventricular arrhythmias.

Three steps to treating hyperkalaemia[10]

Step 1: Reverse the deleterious electrical effects of potassium

(a) Use 5 - 10 ml of 10% calcium chloride or a maximum of 20 ml.
Calcium is only used if the QRS is widened.

Fig 3 - 12-lead electrocardiogram after further intravenous calcium chloride and sodium bicarbonate.



Step 2: Moving potassium intracellularly

(a) 50 ml 50% dextrose over 5-10 minutes with 10 units regular insulin.
(b) 1 mEq/kg body weight of bicarbonate over 10-20 minutes for most patients. Same dose by intravenous push in patients with sine wave QRS pattern or hyperkalaemia with electromechanical dissociation. Bicarbonate is useful in acidotic patients but may have no effect in non-acidotic patients.
(c) Beta agonists – Most studies have used intravenous but not inhaled albuterol. Dose is usually 0.5mg diluted in 100 ml given intravenously over 10-15 minutes. May nebulise in 10-20mg in 4 ml normal saline over 10 minutes.
(d) Magnesium – Dose is 1-2g given intravenously over 5-20 minutes.
(e) Volume – Saline or hypertonic saline helps restore cellular sodium-potassium gradient and is especially good in dehydrated patients.

Step 3: Moving potassium out of the body

(a) Intravenous normal saline 200 ml/hour and frusemide (40 - ?mg) to achieve urine output approaching 150 ml/hour.
(b) Oral calcium resonium A 15g hourly or resonium retention enema 30g, 8 hourly.
(c) Haemodialysis.

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