CHLOROQUINE RESISTANT MALARIA IN CHILDREN FROM
A CHINESE ALBINO FAMILY IN PULAU TEKONG

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There is little transmission of malaria in Singapore, but for the past few years between two and three hundred cases of malaria were notified every year: the great majority of these cases are infected outside Singapore, namely Southern Johore, and the surrounding small islands. In recent years, however, the problem of chloroquine resistant malaria in Western Malaysia (Montgomery, 1963), in Southern Johore (McKelvey, 1968), from Pulau Tekong (Ng, Fung, Colbourne and Gilles, 1969), and further cases in Singapore (Colbourne, Fung and Paul, 1970), has made clinicians feel the need for changing the treatment of falciparum malaria.

Pulau Tekong is well recognised as one of the islands off Singapore where malaria cases are most commonly found. In 1964 and 1965 there were 21 cases, ten times as many, as would have been expected if malaria was evenly spread throughout Singapore; it is difficult to prove whether the cases are infected in Pulau Tekong or Johore, as there is considerable movement of the people between the island and Johore (Ng, Fung, Colbourne and Gilles, 1969). No case of chloroquine resistant malaria has been reported in children in Singapore before, and the following family is interesting in that there were two children from the same family affected with chloroquine resistant malaria.

CASE REPORT

Case 1

C.H.C., a four-year old Chinese boy, was referred on 17.5.69 by the Medical Officer of Health of Pulau Tekong as a case of falciparum malaria, not responding to outpatient treatment. The child was reported to have been sweating for one month, and had fever and rigors for three weeks at home. He was also noted to be lethargic and off-colour. He had been seen by the Medical Officer of Health at Pulau Tekong, and given a total dose of 600 mgms. of chloroquine base orally as an outpatient. There was no proof as to whether the child had taken the tablets regularly although the father said he had given him the tablets as instructed. Physical examination of the child revealed that the general condition of the child was good. He weighed 14.06 kg. which is at the 50th percentile in weight, when compared with Chinese Hong Kong boys of the same age, and his height was 99.1 cm. which is again at the 50th percentile when compared with Hong Kong boys of the same age. The temperature of the child was 37.2°C and there was no pallor. No abnormality was detected in the heart and lungs. The spleen was enlarged to 2 cms. below the left costal margin, and the liver was just palpable. The striking feature of this child was his skin. He was a partial albino or a cutaneous type of albinism. He had a white forelock, brown hair with patchy areas of pigmentation over the arms, legs and face (Fig. 1).

The iris was pigmented and the vision was normal. A peripheral blood film done on admission showed 198 falciparum rings per cu. mm. and a few crescents. The haemoglobin was 10.5 gm.%. The total white cell count was 6,600 per cu. mm., consisting of 76% polymorphs, 14% lymphocytes, 8% monocytes and 2% eosinophils. The packed cell volume was 34% and the immunoglobulin and glucose-six phosphate dehydrogenase level was within normal limits. So that this patient, although he had received treatment as an outpatient in Pulau Tekong, was still having asexual forms of malarial parasite in the peripheral blood. As far as we could gather from the parents, this child had never left Pulau Tekong at all.

Case 2

C.H.M., the brother of the above patient, an eight-year old Chinese boy, was also reported by the father as having had fever and rigors about four weeks prior to admission on 16.5.69. He, too, like his brother, had received 600 mgms. of chloroquine base as an outpatient from the Pulau
Fig. 1. The affected patient, C.H.C., on extreme right with father, and sisters both affected with partial albinism.

Fig. 2. Father of patient with partial albinism.

Fig. 3. Grandfather of patient with partial albinism.

Fig. 4. Patient's aunt affected with partial albinism and three affected siblings with partial albinism from Pulau Ubin.
Tekong outdoor dispensary. Physical examination of this brother revealed a normal looking child with no signs of albinism. His weight was 19.28 kg, which is at the 90th percentile, using Hong Kong Chinese boys weights as standards, and his height was 124.54 cms. which is at the 75th percentile using Hong Kong Chinese boys' height as standards. The temperature was 37.8°C and the general condition of the child was good. The peripheral blood film of this child showed only a few falciparum gametocytes, and there were no trophozoites. The haemoglobin of this child was 10.1 gm.% with a white cell count of 6,700 per cu. mm. and polymorphs 76%, lymphocytes 2%, monocytes 3% and eosinophils 1%. The glucose-six-phosphate dehydrogenase and the immunoglobulin levels were within normal limits. This brother received treatment at Pulau Tekong prior to admission, and on blood examination no asexual malarial parasites but a few gametocytes were seen. This child, too, like his brother, had never been out of Pulau Tekong.

Family Studies

The father of this family was a partial albinos (See Fig. 2) and his peripheral blood film showed no evidence of malaria. Family studies revealed that the father's sister and brother were also partial albinos, living on another island called Pulau Ubin (Fig. 4). The peripheral blood film of these two and their families were negative for malarial parasites. The grandfather of the affected children lived in Singapore and he too was a partial albino (See Fig. 3). Altogether on family studies we found ten partial albinos in three generations, the mode of transmission being a simple dominant mode of inheritance (See Fig. 5). All members of the family had their peripheral blood films examined for malarial parasites and the two members affected were the two children described above.

MANAGEMENT

Both the affected patients were admitted to the Paediatric Unit, Outram Road General Hospital, Singapore, and warded for a period of five weeks, and later transferred to a convalescent home at Changi in Singapore. Blood films were carried out daily on both patients while they were in hospital and on discharge to the convalescent home; and the methods used had been described in a previous paper by Ng, Fung, Colbourne, Gilles (1969). Thick and thin blood films stained with Giemsa were examined for at least 200 fields of the thick films before being declared

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**CHEOW FAMILY WITH PARTIAL ALBINISM. (P133597)**

![Family Tree Diagram]

Fig. 5. Ten affected partial albinos in four generations, showing a dominant mode of inheritance.
negative. Parasite densities were determined by counting parasites against leucocytes in the thick film and converting to parasites per cu. mm. Both children were given chloroquine orally as recommended by the W.H.O. Schedule (1967).

Day 0: First dose—(base) 10 mgs./kg.
Day 1: Second dose—(base) 10 mgs./kg.
Day 2: Third dose—(base) 5 mgs./kg.

Direct supervision by nursing and medical staff ensured ingestion and retention of chloroquine. Urine was tested for chloroquine on the third day of the treatment using Wilson and Edeson's test (1954). Resistance to chloroquine was considered to be present if after the standard course of chloroquine, there was failure to respond within seven days or relapse after the initial response. Resistance was graded according to principles indicated by the World Health Organisation (1967).

**Management of Case 1**

C.H.C., the first patient was observed daily in hospital and treatment was initiated on the 13th day after admission to hospital on 28.5.69 when the peripheral blood film showed 462 trophozoites per cu. mm. (Fig. 6). The temperature was 36.7°C and the spleen was 1½ cms. below the left costal margin. The next day there were 5,000 rings per cu. mm. and the following day the count dropped to 99 rings per cu. mm. The urine was positive to chloroquine on the third day of the test ensuring that the child had absorbed the drug. From the first of June 1969 to the sixth of June 1969, the child was afebrile and well. The spleen was enlarged to 1 cm. below the left costal margin and the peripheral blood film showed no rings and no crescents. On 7.6.69 exactly six days after he had completed the course of chloroquine, the child showed 528 falciparum rings per cu. mm. and on 11.6.69 there were 13,629 rings per cu. mm. (Fig. 6). This suggested R1 type of resistance to chloroquine, because he

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**CHEOW H. CHEONG — CHLOROQUINE RESISTANT MALARIA IN A PARTIAL ALBINO.**

![Graph showing the progression of case management](image)

**Fig. 6.**
CHEOW HOCK MING — CHLOROQUINE RESISTANT MALARIA FROM PULAU TEKONG.

SIZE OF SPLEEN

- Spleen just palpable
- Spleen n.p.
- Spleen palpable
- Spleen 2 cm

TEMPERATURE

- 101°F.
- 100°F.
- 99°F.
- 98°F.

CHLOROQUINE

- 800 mgs

TROPHozoites

- Per cub mm

- 10,000
- 5,000
- 2,000

MONTH

- MAY
- JUNE
- JULY

DAYS

- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10
- 11
- 12
- 13
- 14
- 15
- 16
- 17
- 18
- 19
- 20
- 21
- 22
- 23
- 24
- 25
- 26
- 27
- 28
- 29
- 30
- 31

Hb 10.1 gm%
Hb 12 gm%
Hb 12.2 gm%
Hb 12.3 gm%
Hb 13 gm%

Fig. 7.
showed clearance of the asexual parasitaemia followed by recrudescence within 28 days according to the W.H.O. definition. The patient, therefore, was started on Bactrim tablets 1 tab. b.d. on 14.6.69 (1 tablet of bactrim contains 20 mgms. of Trimethoprim and 100 mgms. of Sulphomethoxazole) for two days. The peripheral blood film was free of trophozoites on 16.6.69 and continued to be free of trophozoites till 26.6.69 when he was transferred to the convalescent home at Changi in Singapore. Daily peripheral blood films were taken by the matron there, and the films were examined in the Department of Social Medicine and Public Health. The peripheral blood films did not show any trophozoites except for one or two crescents. This picture continued till 31.7.69, when he was discharged and sent home to Pulau Tekong. Thereafter, he was followed as an out-patient from Pulau Tekong at the Department of Paediatrics, Outram Road General Hospital, Singapore, and on his last check-up on 30.9.70 he was quite well and had been free of fever for one year. The peripheral blood films too were negative, and his haemoglobin was 12·1 gm.%.

Management of Case 2

C.H.M., the eight-year old brother, was admitted together with C.H.C. on 17.5.69, having received chloroquine prior to admission as an out-patient at Pulau Tekong. His temperature was 37·78°C and the spleen was just palpable. The peripheral blood film showed no evidence of any malarial parasite for twenty-three days. On 9.6.69, the peripheral blood film showed 4,908 rings per cu. mm. The child was given a total dose of 375 mgms. of chloroquine base and on the third day of treatment the urine was positive for chloroquine. The rings forms disappeared soon after this course of chloroquine but reappeared on the sixth day of treatment (Fig. 7). On the 19th of June 1969, the trophozoite count was 268 trophozoites per cu. mm. and soon after this the ring forms rose to 13,735 rings per cu. mm. He, too, like his brother showed the R1 type of resistance to chloroquine. The child was treated with Bactrim, one tablet twice a day for two days and as the number of trophozoites did not clear up completely, he was given a second course of Bactrim on 30.6.69 and 1.7.69. However, on 5.7.69 when the peripheral blood film showed 1,474 falciparum rings per cu. mm. he was given Fansil and Pyrimethamine (Fansil is sulphomethoxine 500 mgms.). These ring forms still persisted and eventually on 21.7.69 when the trophozoite count was 1,239 falciparum rings per cu. mm. he was given Mist Quinine Sulphate grain VII t.d.s. with Dapsone 10 mgms. t.d.s. and Pyrimethamine 25 mgms. o.m. for 3 days. The falciparum rings disappeared and a few crescents persisted for a few days. On discharge from the convalescent home on 31.7.69 the child was followed up monthly, and since his discharge the peripheral blood film has been free of trophozoites. He was last seen as an out-patient on 30.9.70 and was quite well with a haemoglobin of 12 gm.%.

DISCUSSION

These two patients are interesting from two points of view, firstly the inheritance of partial albinism in a simple autosomal dominant fashion through three generations, and secondly, the problem of chloroquine resistance malaria in children.

We will consider the first problem, partial albinism. There are three types of albinism, namely oculocutaneous or complete albinism, ocular albinism and cutaneous or partial albinism. Total albinism is inherited as an autosomal recessive condition where the parents are phenotypically quite normal. Ocular albinism is inherited as a sex-linked condition and cutaneous or partial albinism as a simple dominant condition.

It is still uncertain as to what are the factors responsible for albinism. In the majority of cases albinism is not due to lack of melanocytes. Brestnach et al quoted by Fitzpatrick and Querado, Jr. (1964) demonstrated the presence of Langerhan's cells at the dermal-epidermal junction of the skin from the hypopigmented areas of persons with cutaneous albinism. They consider that these cells may be converted to melanocytes and this accounts for the repigmentation in affected areas of skin with age. In cutaneous albinism factors which prevent the conversion of Langerhan's cells to melanocytes may be partly responsible for the defect. In cutaneous or partial albinism, there are bilateral triangular white "forelocks" which fuse in the midline, and the scalp under this is white also. All our albino patients had this white forelock. On the trunk anteriorly hypopigmented areas were seen from the nipples down to the iliac fossa, and posteriorly there was always an area of normal pigmentation. Over the limbs the distribution of the hypopigmented areas are from the middle part of the upper arm to the wrist and from the mid-thigh to mid-calf on both the flexor and extensor surfaces. In the cutaneous form of albinism there is a tendency for pigmentation to occur in the involved areas with age, and this return to pigmentation suggests a return of the melanocytes in this form to become active again. The mode of transmission of this form of inheritance was a
simple dominant mode and affected members occurred in each generation. The great grandparents were in China, and it was not known whether any of them were partial albinos.

The second problem in this family was that of chloroquine resistance malaria. There was no doubt that both the patients above exhibited drug resistance. Drug resistance W.H.O. (1967) has been defined as the ability of a parasite strain to multiply or to survive in the presence of a concentration of a drug that normally destroys parasites of the same species or prevents their multiplication. Such resistance may be relative (yielding to increased doses of the drug tolerated by the host) or complete (withstanding maximum doses tolerated by the host). Both the patients described were followed up very carefully and they both conformed to the R1 type of resistance as defined by W.H.O. (1967). In both cases, although we are not quite certain as to whether the children consumed all the chloroquine in Pulau Tekong, the course of chloroquine they received in the wards was the second course of chloroquine. The recrudescence in both cases was accompanied by a rise in the parasite (ring) count, and symptoms of fever and rigors.

Case 1 responded very well to Bactrim (i.e. Trimethoprim and Sulphamethoxazole).

Case 2 proved resistant not only to two courses of Bactrim but also to Fansil and Pyrimethamine and eventually cleared with Quinine, Dapsone and Pyrimethamine. According to the W.H.O. expert committee on Malaria (1968) they recommend quinine sulphate (2 gms. daily in divided doses for seven to ten days) for chloroquine resistant malaria, and the subsequent administration of primaquine or pyrimethamine for a gameticidal or sporontocidal effect. Among the long-acting sulphonamide compounds, sulfontequine has been most frequently used, either alone or in combination with pyrimethamine given in one or two doses. The W.H.O. expert committee (1968) report a high percentage of cures in Thailand with a single dose of 1-0 gm. of sulfontequine with 50 mgms. of pyrimethamine for chloroquine resistant malaria. In Singapore, Colbourne, Fung and Paul (1970) found that about half the patients admitted with Plasmodium falciparum were resistant to chloroquine. This amount of resistance was similar to the findings of McKelvey (1968) who found that half the British servicemen infected with Plasmodium falciparum in various parts of Western Malaysia were resistant to chloroquine at the R1 or R2 level. Although we have not been faced with chloroquine resistant malaria in children in Singapore before, it would be important to think of this problem and treat cases appropriately when cases of Plasmodium falciparum infections occur.

There is no known connection between albinism and chloroquine resistance malaria.

**SUMMARY**

Two children with chloroquine resistant malaria are described, both from an island off Singapore called Pulau Tekong. One of the children was a partial albino and family studies revealed ten partial albinos in three generations transmitted in a dominant mode of inheritance. A brief description is given of the factors responsible for partial albinism. One child with chloroquine resistant malaria responded to Trimethoprim and Sulphamethoxazole, while the other case was more resistant and eventually responded to Quinine, Dapsone and Pyrimethamine.

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**REFERENCES**