

PostScript

LETTERS

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Miconazole and clobazam; a useful interaction in Dravet's syndrome?

Chiron and the STICLO study group report a dramatic improvement in seizure control in children with severe myoclonic epilepsy in infancy or Dravet's syndrome (DS) when treated with valproate, clobazam, and stiripentol.¹ Stiripentol inhibits the metabolism of clobazam and its metabolite norclobazam by P450 cytochromes.

SM, 9 year old girl with DS and severe developmental delay had poor seizure control and frequent status epilepticus despite various combinations of antiepileptic medicines, most recently lamotrigine 35 mg/kg/day and nitrazepam 0.8 mg/kg/day. Careful seizure diaries were kept by her mother CM while lamotrigine and nitrazepam were slowly withdrawn and valproate and clobazam were introduced. Several 14 day courses of miconazole 2% oral gel were given SM for oral thrush. During each course CM observed that SM's seizure control improved remarkably, and she progressed from being wheelchair bound to standing and displaying more interest in her environment. No unwanted side effects of this treatment were observed. Miconazole is partly absorbed orally, and inhibits P450 cytochromes including isoenzymes 3A4 and 2C9,² causing interactions with antiepileptic medicines including benzodiazepines.³ We hypothesised that miconazole may have a similar action to stiripentol when given with valproate and clobazam in DS.

With CM's informed consent, we analysed steady state trough plasma levels of valproate, nitrazepam, clobazam and the metabolites aminonitrazepam and norclobazam while SM was taking these medicines (baseline) and then while taking added miconazole (day 22) or stiripentol (day 50) (see table 1). The analyses were performed by MH, SD, and RB using liquid chromatography-tandem mass spectrometry, except for valproate, where gas chromatography-mass spectrometry was used. The results show markedly increased levels of norclobazam during miconazole or stiripentol treatment compared with baseline, similar to Chiron's

Table 1 Table of results

	Day 1	Day 22	Day 50
Drug			
Miconazole 2% gel (from day 9 to day 23)		2.5 ml tds	
Stiripentol (mg/kg/day) (from day 36 onwards)			50
Nitrazepam (mg/kg/day)	0.45	0.40	0.40
Clobazam (mg/kg/day)	1.0	1.0	0.5
Valproate (mg/kg/day)	24	24	24
Seizures in preceding week	14	2	2
Toxicology results			
Miconazole (mg/l)		~0.02	
Nitrazepam (µg/l)	120	150	120
Aminonitrazepam (µg/l)	40	42	44
Clobazam (mg/l)	0.54	1.0	1.0
Norclobazam (mg/l)	2.6	17	10
Valproate (mg/l)	49	79	68

results for stiripentol, which supports our hypothesis.

The safety of long term miconazole use is unknown. Literature searches and correspondence with the distributor of miconazole in New Zealand (Janssen-Cilag Pty Ltd, 4 March 2002) have identified no studies of long term miconazole use in children, nor has this interaction between clobazam and miconazole been reported.⁴ Miconazole may be a useful medication in DS for trialling the possible benefits of stiripentol when the latter is not readily available, when stiripentol cannot be tolerated,⁵ or during episodes of fever when children with DS are more likely to develop status epilepticus. Miconazole and stiripentol are also likely to interact with other medicines used in children with DS. This interesting and potentially useful interaction warrants further cautious study.

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Fever phobia revisited

The National Coordinating Centre for Health Technology Assessment recently issued a commissioning brief calling for proposals to look at "the clinical effectiveness of paracetamol alone, ibuprofen alone, and paracetamol and ibuprofen in combination in the management of fever in pre-school children".¹ This call raises a number of issues regarding the use of such drug combinations in the treatment of febrile children.

Fever phobia is a term that was coined some years ago to describe exaggerated fears that parents have about fever in children. At the time the original research was done these fears included brain damage, seizures, death, coma, and blindness. Twenty years later many of these fears remain,² leading to the possibility of over-aggressive treatment and unnecessary worry.

As there is no evidence that fever, as distinct from hyperthermia, causes any harm, therapy is usually aimed at promoting comfort rather than the aggressive pursuit of normothermia. It is somewhat surprising therefore that the HTA are pursuing a line of enquiry that might reinforce fever phobia through the promotion of combination antipyretic therapy. Furthermore, by using two drugs where one was used previously, the chance of parents making an error in administration increases.

Perhaps most worryingly, there is cause for concern about the safety of the combined use of these two drugs, as renal failure has been reported in a child taking this combination. Although not conclusively demonstrated to be the cause, two mechanisms by which the drugs may have acted synergistically to cause this damage have been proposed. The first is that renal damage may occur as the result of the accumulation of oxidative metabolites of paracetamol in the renal medulla during renal ischaemia caused by ibuprofen, while the second concerns the inhibition of urinary prostaglandin synthesis which may also cause renal damage. It is hypothesised that these may be exacerbated by mild to moderate dehydration.³

Such negative outcomes, even if rare, are of particular concern because there is no need to combine paracetamol and ibuprofen in this way. If antipyresis or analgesia is required there are existing safe treatments in the form of the two drugs separately, and so the combined use of paracetamol and ibuprofen is simply unnecessary. The HTA should therefore reconsider this call, and redirect the resources to the many other urgent projects that require funding.

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Juvenile myasthenia gravis mimicking recurrent VI nerve palsy of childhood

A 5 year old Asian boy presented to the paediatrician with diplopia following ear ache. Isolated VI nerve palsy was suspected. Full blood count, ESR, magnetic resonance imaging (MRI), and ENT examination were normal. He recovered within a week, but subsequently suffered six episodes of transient convergent squint with abduction deficit. He was referred to our neurologist for further opinion.

His developmental milestones, family history, and ocular and general examination as well as investigations were normal apart from vitiligo around the lids. At subsequent consultation, a right convergent squint was noted

but with apparent full ocular movements. AchR Ab titres, performed this time, were weakly positive at 25×10^{10} M ($< 5 \times 10^{10}$ M = negative and $5–50 \times 10^{10}$ M = positive).

Ophthalmic evaluation at this stage revealed visual acuities of 6/12 (right), and 6/7.5 (left), intermittent alternating convergent squint, normal ocular movements, motor fusion, and refraction. His orbicularis oculi function was weak, but no lid twitch or ptosis on sustained upgaze was elicited. Cold stimulation by ice pack test² showed a transient improvement in orbicularis function, but no change in his strabismus. Repetitive stimulation electromyogram (EMG) of orbicularis oculi was normal, but single fibre EMG could not be done as the child became very distressed. Saccadic studies³ showed longer and slower saccades which strongly suggested myasthenia (fig 1).

The clinical features, saccadic studies, positive antibody titres, and the association of vitiligo confirmed the diagnosis of ocular myasthenia. During the follow up, his AchR Ab levels, interestingly, were negative. Benign idiopathic VI nerve palsy,¹ sometimes recurrent, is a diagnosis of exclusion. Variable strabismus is a known feature of myasthenia gravis. Elevated AchR Ab is the hall mark of myasthenia; however, it may be low to normal in younger age, boys, and in ocular myasthenia. Periocular single fibre EMG is often difficult and stressful to perform in younger children. The tenson test needs a frank clinical sign to demonstrate the improvement. The ice pack test is helpful as shown by improvement in his orbicularis strength. Strabismus is known to be resistant to cold stimulation by ice pack compared with ptosis.² The saccadic velocity pattern of myasthenia differs from paralysis or restrictive problems.³ The myasthenic eye can reach a normal peak saccadic velocity, but cannot sustain it.

This report highlights the difficulty in diagnosing some ocular myasthenia and the

value of saccadic studies, which are simple, non-invasive, and repeatable.

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RCPCH guideline appraisal on EEG after first seizure

A recent RCPCH guideline appraisal asserted: "There is no need for an EEG following a first simple afebrile seizure".¹ This is puzzling. A "simple afebrile seizure" is not an entity recognised in the ILAE diagnostic scheme.² More importantly, we disagree both with the recommendation and the contention that it is based on grade B evidence.

The recommendation is principally based on a meta-analysis by Gilbert and Buncher, which found the sensitivity and specificity of EEG in helping to predict recurrence after a first seizure to be too low to justify its routine use.³ However, they concluded: "EEG should be ordered selectively, not routinely, after first unprovoked seizure in childhood", which is different from, "There is no need for ...". Moreover, the principle purpose of performing an EEG after a first seizure is not to predict recurrence.

There are many different disorders in which a seizure may be the first symptom. While it may be useful for statistical purposes to lump these together, clinically this is indefensible. There are many common scenarios when, following an initial generalised tonic-clonic seizure (GTCS), an EEG may be helpful for diagnostic, therapeutic, and/or prognostic purposes. This may be the case if one suspects a benign focal seizure disorder, a photically induced seizure, or an idiopathic generalised epilepsy in which the first GTCS may have been preceded by hundreds of unrecognised minor seizures.

The guideline might be better worded: "An EEG following a first definite seizure may not yield useful information regarding recurrence risk, but may provide useful information regarding syndrome diagnosis, the role of precipitating factors, and management. The need for an EEG should be determined following clinical evaluation by a clinician with expertise in seizure disorders". In this the guideline would reflect other evidence based guidelines that EEG should be "... part of the neurodiagnostic evaluation of the child with an apparent first unprovoked seizure".⁴

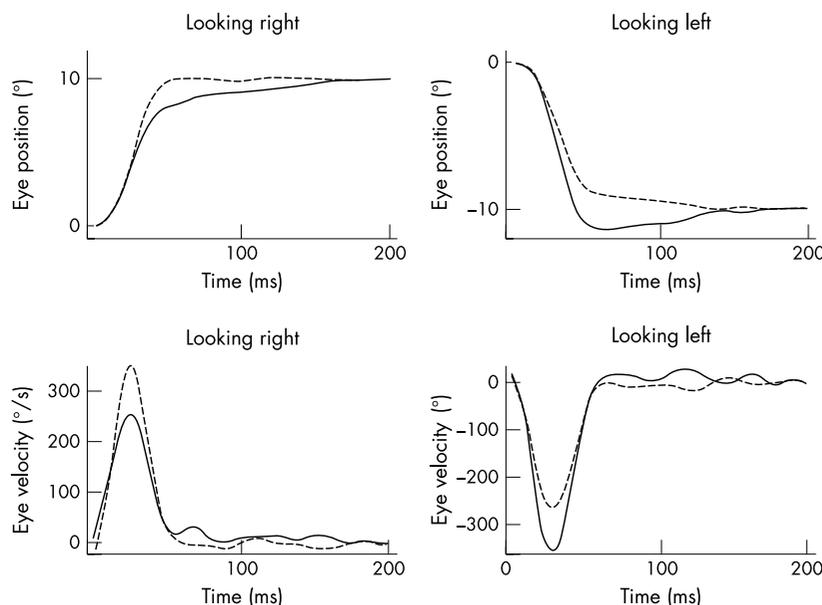


Figure 1 Eye position and velocity during 10° saccades from the midline. The traces show the averages over 10 saccades. The position and velocity of the right eye is shown by a continuous line, while that of the left eye is shown by a dashed line. After an initial rapid movement, saccades into the field of action of the lateral rectus drift slowly towards their target direction. (Courtesy of R Clements)

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Severe vitamin D deficient rickets in black Afro-Caribbean children

Concern has been raised over the past few years, at the prevalence of rickets in British Asian children¹ and recent immigrants to the UK.² Here we describe five cases of severe rickets in children of second generation Black-African or Caribbean parents who presented to paediatric outpatients in a socially deprived area of inner London. Weaning had been unsuccessful in all of the cases. The affected children all had biochemical (table 1) and radiological evidence of severe rickets.

Case 1

This child was referred to clinic by his GP due to delay in walking. His mother was still breast feeding as he refused to drink cows' milk. Solids had been introduced at 6 months of age but he was a "fussy" eater. His mother was also on a restricted diet for weight reduction. He looked well but had wrist swelling and his anterior fontanelle was still patent. His weight was on the 25th centile.

Case 2

This child was referred by her GP with an abnormal gait and bowing of her legs. She was breast fed till 1 year of age. From 3 months of age, her mother had excluded



Figure 1 Radiograph of the legs from case 2 showing bilateral distal tibial varus procurvatum deformity.

dairy products from her own diet due to concerns regarding milk allergies. From 1 year of age, the child had not received any dairy products. She had swelling of her wrist and ankle joints and a very wide shuffling gait with marked varus deformity and bowing of her legs (fig 1). Her anterior fontanelle was still patent. Height and weight were both on the 25th centile.

Case 3

This child was referred to paediatric outpatients following several visits to the casualty department with recurrent fevers. She had been fully breast fed since birth. Her mother did not drink milk. She had tried to introduce solids into the child's diet from 5 months of age without success. The child looked pale and had swollen wrists and knees. Her weight was just below the 2nd centile compared with the 9th centile at birth.

Case 4

This child was referred by his GP with possible rickets. His mother described him

as a very poor eater and he was still exclusively breast fed. His mother was taking a full mixed diet. On examination he had marked genu varum and swelling of his wrists. His weight was on the 0.4th centile compared to the 9th centile at birth.

Case 5

This child was referred with failure to thrive and severe eczema. She had been gaining weight satisfactorily until 3 months of age, when she developed severe facial eczema. She had been exclusively breast fed until 6 months when she was put on Neocate formula feeds which she did not seem to tolerate. She also refused to take solids. Her mother had been avoiding dairy products in her own diet in order to avoid passing on cows' milk allergens. The infant's weight was below the 0.4th centile compared to the 50th centile at birth. She had hypergammaglobulinaemia with an IgG of 44.4 g/l (normal range 4.1–10.9 g/l) and an iron deficient anaemia. A RAST test was positive for cows' milk. She was HIV negative. Her hypergammaglobulinaemia resolved as the eczema improved. Of note, her mother had low levels of 25(OH)D (7.4 ng/l) and phosphate (0.65 mmol/l).

Discussion

Responses to a recent questionnaire sent to paediatricians in the West Midlands suggest that rickets is being seen in the Afro-Caribbean population.³ However, most attention has been given to the risk of rickets in the Asian population in the UK. Most vitamin D is obtained from the action of sunlight on the skin as 7-dehydrocholesterol is converted to cholecalciferol (vitamin D₃). Undoubtedly increased skin pigmentation would have played a role in the decreased levels of vitamin D shown in the present cases.⁴ However, none of the mothers were following the Islamic custom of veil wearing which can further reduce vitamin D levels.⁵ Four of the five cases were exclusively breast fed. As there is relatively little vitamin D in breast milk, it has been recommended that lactating women should supplement their diets with vitamin D (10 µg daily).⁶ Weaning can be associated with a lowering in vitamin D levels. Although some commercially available weaning foods have added vitamin D, it is recommended that children under 2 years of age should receive additional supplementary vitamin D of 7 µg per day.⁶ None of the children or mothers in this series were receiving vitamin supplementation prior to

Table 1 Biochemical bone profiles and characteristics of infants at presentation

Case no.	Ethnic group	Birth weight (kg)	Sex	Gestation (wk)	Birth order	Age at weaning (mth)	Age at presentation (mth)	Calcium (mmol/l) (2.2–2.6)	Phosphate (mmol/l) (1.3–2.5)	Alkaline phosphatase (IU/l) (30–130)	25(OH)D (ng/l) (10–42)	Hb (g/l) (99–141)
1	Black-Caribbean	3.1	Male	40	2/2	6	17	2.2	0.72	2040	4.0	113
2	Black-Caribbean	2.7	Female	38	2/3	6	21	2.3	0.9	3180	4.4	114
3	Black-Caribbean	2.8	Female	40	2/2	4	16	2.5	0.85	2828	6.6	118
4	Black-Caribbean	3.1	Male	40	3/3	5	13	2.2	0.87	2484	7.4	110
5	Black-African	3.3	Female	39	1/1	4	10	2.4	0.75	2465	8.5	88

referral. Four of the children have responded to treatment with vitamin D₃ 6000 units/day. In one case, there have been problems with parental compliance. In all the cases, the index of suspicion for rickets had been low, thus delaying referral and treatment. Awareness of rickets in the Black-African and Caribbean population needs to be raised in health visitors, GPs, and parents.

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Hyperchloraemic acidosis consistent with ammonium chloride administration

We report an infant with recurrent self limiting hyperchloraemic acidosis. This 1 month old girl was admitted with vomiting, decreased feeding, and rapid breathing. On examination she was lethargic and tachypnoeic with normal blood pressure and peripheral perfusion. Investigations revealed uncompensated metabolic acidosis and uraemia (table 1). She was managed with antibiotics and sodium bicarbonate and showed rapid improvement in acidosis and uraemia in 48 hours. Following discharge she was brought to the outpatient department on multiple occasions with vomiting, failure to thrive, and tachypnoea. She was readmitted

at the age of 4 months with lethargy, tachypnoea, uncompensated hyperchloraemic acidosis, and uraemia. She was managed with antibiotics and sodium bicarbonate; the biochemical parameters normalised over 52 hours.

Negative urinary anion gap, normal urinary to blood CO₂ difference, and fractional excretion of bicarbonate excluded distal and proximal renal tubular acidosis in this child.¹ Acidic urine in the presence of systemic acidosis and extremely high levels of serum and urinary chloride pointed to a chloride load overwhelming renal excretory capabilities.² Negative anion gap of -17.6 mmol/l indicated an excess of unmeasured cation to the level of 30 mmol/l. This, combined with transient increase of urea with normal levels of creatinine and renal ultrasound indicated the possibility of ammonium (NH₄⁺) load, and the clinicolaboratory picture of the child was explained on the basis of ammonium chloride load. Chloride levels of the milk and water given to the child as well as blood gas and serum chloride levels in the parents were normal.

Ammonium chloride is used in the metal-lurgy industry in our city and is readily available. The possibility of Munchausen by proxy syndrome was therefore considered once investigations for environmental overload were non-contributory; this however could not be proved as the mother repeatedly denied administration of ammonium chloride. The child was discharged on normal feeding without any treatment. At three months follow up the child was growing normally, and did not have tachypnoea, vomiting, or acidosis. The findings of this case are suggestive of exogenous ammonium chloride administration, a possibility that should be considered in unexplained hyperchloraemic metabolic acidosis with negative urinary anion gap and high urinary chloride levels.

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Voiding dysfunction in Duchenne muscular dystrophy

We read with interest the report by MacLeod *et al* who described urinary symptoms in 46 (62%) of 74 male children with Duchenne muscular dystrophy (DMD).¹

The authors comment that "The neurological basis for this dysfunction is difficult to explain." Daytime incontinence, urinary frequency, and urgency were reported in 22 (48%), 14 (30%), and 18 (39%) of the 46 boys, respectively. These symptoms suggest the possibility of urge syndrome, a common problem in children that does not have any obvious neurological cause. The pathogenesis of urge syndrome is incompletely understood, but voiding postponement is common in these children and might play an aetiological role.² Voiding postponement is more common in children with neuromuscular disorders because the physical disability impairs access to a bathroom. There are many reasons why access to a bathroom is impaired or why these children might choose to postpone voiding. Wheelchair patients require specialized bathroom facilities and might require assistance, neither of which might be available. Even for "ambulatory" patients, getting on and off a toilet is often a labour-intensive and time-consuming process for many of these children. Requesting assistance for such a personal task might be difficult or embarrassing for some children.

Children with urge syndrome commonly demonstrate squatting behaviour, which is a learned response to minimize incontinence associated with an unwelcome detrusor contraction. Children with DMD have proximal muscle weakness and might be limited in their ability to squat or otherwise to develop muscular strategies to cope with an unwelcome detrusor contraction.

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Table 1 Laboratory findings in the child

Parameter	First admission			Second admission			Normal values
	Admission	28 hours	72 hours	Admission	28 hours	72 hours	
pH	6.95	7.332	7.407	7.10	7.358	7.414	7.35-7.45
Bicarbonate (mmol/l)	4.8	15.2	21	9.6	22.3	22.3	22-24
Base excess (mmol/l)	-25.3	-7.2	-4	-15	-5.3	-1.2	±2
Sodium (mEq/l)	152	145	143	133	138	134	135-145
Potassium (mEq/l)	2.8	3.3	3.5	3.1	3.3	3.4	3.5-4.5
Chloride (mEq/l)	-	-	-	141	110	97	95-100
Anion gap (mEq/l)	-	-	-	-17.6	9.7	13.7	10±2
Urine chloride (mEq/l)	-	-	-	156	110	106	
Urea (mg/dl)	162	60	23	120	55	14	7-18
Creatinine (mg/dl)	0.4	-	0.3	0.3	-	0.3	0.2-0.4
Urine net charge*	-	-	-	-20	-18	-11	
Urine pH†	-	-	-	5.2	6.6	7.7	

*Urine net charge = urinary sodium + urinary potassium - urinary chloride. Positive, RTA; negative, extra-renal loss/acid load.

†Urinary pH in the presence of metabolic acidosis: <5.5, proximal RTA/acid load; >5.5, distal RTA.

Prevention of hyponatraemia

At least two children in Northern Ireland have died in recent years as a result of severe hyponatraemia (serum sodium <130 mmol/l).¹ Death or neurological morbidity related to this condition has been reported in more than 50 children.² Although risk factors include vomiting, pain, anxiety, disturbances of the central nervous system, and metabolic and endocrine disorders, it has become recognised that any child receiving intravenous fluids or oral rehydration is potentially at risk.³ The particular risks associated with the postoperative period were highlighted by Arieff in 1998, who pointed out that plasma levels of vasopressin (antidiuretic hormone, ADH) are raised in virtually every child in the postoperative period.⁴ If such children are given fluids containing less than 140 mmol/l of sodium there will always be a tendency towards postoperative hyponatraemia.

A solution containing 0.18% sodium chloride in 4% glucose is commonly used in paediatric practice and is generally held to be isotonic. However, in the catabolic child the glucose is metabolised rapidly, causing the fluid to become hypotonic *in vivo*, with the potential for significant fluid shifts. If the child is in the postoperative period or in any other situation where there is a high level of circulating vasopressin, a situation can arise where excess free water is retained within the circulation. This can be compounded by water effectively administered in the intravenous fluids. This condition has been called "dilutional hyponatraemia" because the "free" water component of the serum has increased, causing dilution of the major

cation, sodium. This "free" water will pass rapidly and unhindered across cell membranes with the particular risk of development of cerebral oedema. Children may be at particular risk of brain damage due to increase in intracranial pressure in this situation.²

A working group in Northern Ireland has developed guidelines which have been published by the Department of Health Social Services and Public Safety.³ These guidelines emphasise that every child receiving intravenous fluids requires a thorough baseline assessment, that fluid requirements should be assessed by a doctor competent in determining a child's fluid requirement, and fluid balance rigorously monitored. The value of accurate measurement of weight, and monitoring of urea and electrolytes, in any child requiring prescribed fluids after 12 hours is emphasised, together with the importance of assessment of fluid balance and prescription at least every 12 hours by an experienced member of clinical staff.

This must take account of all oral and intravenous intake, together with the measurement and recording of all losses (including urine, vomiting, diarrhoea, etc) as accurately as possible.

Replacement fluids must reflect fluid loss, and in most situations this will imply a minimum sodium content of 130 mmol/l. This must be considered and prescribed separately, reflecting the fluid loss in both volume and composition. In some situations laboratory analysis of the electrolyte content of the fluid lost may be helpful. It is important to remember that, while children receiving intravenous fluids are at particular

risk, children receiving oral rehydrating fluids may also be at risk, as these are often also hypotonic. Vigilance is therefore required for all children receiving fluids. Medical and nursing staff need to be aware of risks in this situation, and of early signs of developing cerebral oedema such as vomiting, deteriorating level of consciousness, or headache, before more serious symptoms such as seizures occur, as deterioration to this extent is associated with significant morbidity and mortality.

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Miliaria crystallina complicating staphylococcal scalded skin syndrome



A 7 year old male child was admitted to our hospital during the summer with staphylococcal scalded skin syndrome (SSSS). After five days of appropriate treatment, he was to be discharged. Unexpectedly, while he was playing in the ward, his skin suddenly erupted with crops of clear, 2–10 mm, waterdrop-like vesicles as we watched. The parents and nursing staff became anxious as the vesicles were extremely fragile and broke with the slightest touch. They also involved previously unblistered skin. This seemed typical of miliaria crystallina except for the size.² After reassurance, he was sent home. The rash lasted for 18 hours and resolved spontaneously by peeling.

Miliaria crystallina is a transient occlusive sweat gland disorder resulting in the leakage and retention of sweat into the epidermis.¹ It is characterised by diffuse eruption of extremely fragile, asymptomatic, epidermal, 1–3 mm size, waterdrop-like vesicles which appear in crops on a non-inflammatory base.² It is seen commonly during the neonatal period and rarely, presents congenitally.¹ In children and adults, it can be seen in febrile illnesses due to increased sweating and also following the use of drugs including bethanechol³ and isotretinoin.⁴ Miliaria has been hypothesised to be due to sweat duct disruption and occurs when a potential space develops between the affected epidermal cells and the new proliferating cells beneath them.⁵

In our patient, we postulate that staphylococcal toxins weakened the epidermis, creating a potential space. His increased activity while playing led to pooling of sweat in this space which manifested as miliaria crystallina. We would like to remind paediatricians of the occurrence of this self limiting, harmless, but sometimes alarming disorder in any fever, although in SSSS there is a particular reason for the spread of the lesions.

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