


# A 4-Year-Old Boy With Shortness of Breath

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## Case Report

A 4-year-old boy presented to the general practitioner (GP) with a 24-hour history of progressively worsening shortness of breath (SOB). Over this time period, a productive cough and fever had also developed. The patient had no history of respiratory disease and there were no sick contacts. For the last fortnight, however, his mother reported that he has “not been his usual self”: appearing disinterested and lethargic. This was accompanied by considerably increased levels of thirst. On examination, the patient was mildly pyrexia (37.1°C) and tachypneic (32 breaths per minute), short (measuring <2nd decile), had wide-set nipples, hypoplastic toenails, small cup-like ears, and a calcaneovalgus deformity. The syndromic appearance was explained by a known genetic abnormality—trisomy 9p. No other significant examination findings were present, with clear respiratory sounds audible throughout the lung fields. The GP reached a diagnosis of bacterial lobar pneumonia, discharging the patient with a course of amoxicillin.

The following day, the patient presented to the Accident and Emergency Department with SOB, confusion, nausea, vomiting, polydipsia, polyuria, and abnormally scented breath. A bedside glucose measurement was immediately obtained, revealing a blood glucose of 41.6 mmol/L (748.8 mg/dL). The patient’s temperature was 37.5°C, and respiratory rate was 40 breaths per minute. An arterial blood gas revealed a blood pH of 7.24, bicarbonate of 13.7 mmol/L (246.6 mg/dL), blood glucose of 29.3 mmol/L (527.4 mg/dL), and ketones of 7.8 mmol/L. A diagnosis of diabetic ketoacidosis (DKA) was made, and the child was immediately transferred to the Pediatric Observation Unit.

## Final Diagnosis

DKA in a patient with underlying trisomy 9p.

## Hospital Course

Initially, a resuscitation volume of 260 mL of 0.9% saline with 10 mmol KCl was administered. In following, the patient was then placed on maintenance fluids. Insulin was administered 1 hour after fluid resuscitation, starting at a rate of 0.65 mL/h (child weight: 13.1 kg [29 lb]). Two-hourly monitoring was scheduled. At 2 hours following administration of resuscitation fluids, the patient’s blood glucose remained static at 29.3 mmol/L (527.4 mg/dL). As such, the insulin dose was raised to 1.3 mL/h in accordance with local DKA protocols.

At 4 hours following administration of resuscitation fluids, the patient’s blood glucose had reduced to 14.8 mmol/L (266.4 mg/dL). However, his temperature continued to rise, reaching a high point of 38.5°C 12 hours following admission. At this point, the blood glucose had risen back to 23.2 mmol/L (417.6 mg/dL). Blood cultures were then performed, revealing coagulase-negative staphylococci. This was treated with intravenous flucloxacillin and ceftriaxone. Following administration of antibiotics, the patient improved significantly. His blood glucose continued to fall (7.8 mmol/L [140.4 mg/dL] at day 3 [see Figure 1]), and the patient was discharged on day 5 of admission with continuous subcutaneous insulin infusion therapy.

During admission, tests for thyroid autoantibodies and coeliac disease were negative. However, the patient’s mother has been unresponsive to requests to determine diabetic etiology.

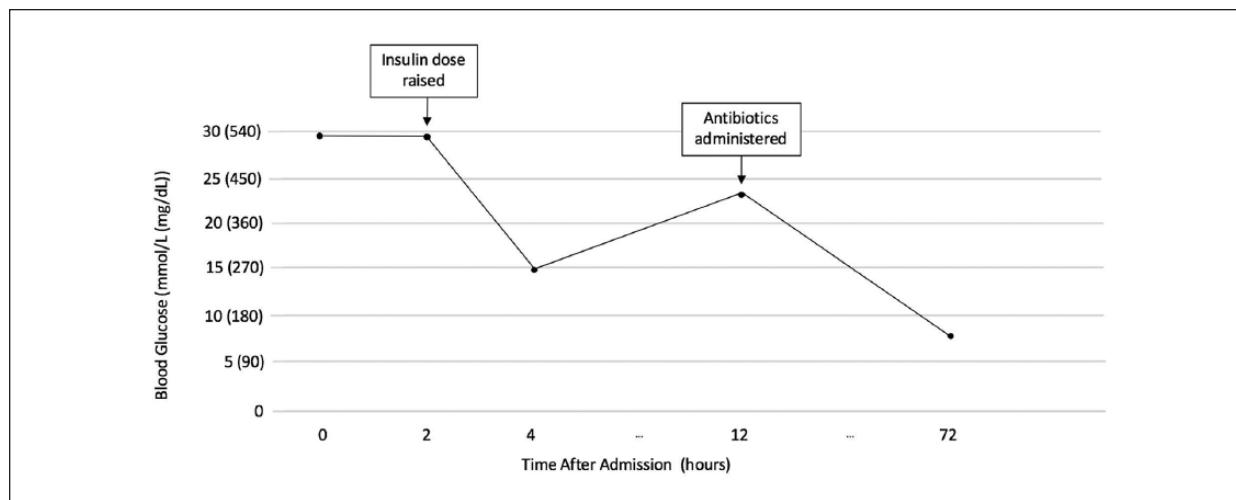
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**Figure 1.** A graph demonstrating the patient's blood glucose levels against time after admission.

**Table 1.** Presenting Features of DKA<sup>1</sup>.

Stage	Signs and Symptoms
Early	Polyuria
	Polydipsia
	Nausea
	Malaise
	Abdominal pain
Late	SOB
	Tachycardia
	Tachypnea
	Vomiting
	Dizziness
	Pear-drop breath
	Confusion
Reduced consciousness	

Abbreviations: DKA, diabetic ketoacidosis; SOB, shortness of breath.

## Discussion

This case raises interesting points for discussion related to both DKA and trisomy 9p.

### Diabetic Ketoacidosis

DKA is a metabolic complication of type 1 diabetes mellitus presenting with a range of symptoms listed in Table 1.

A lack of insulin results in an inability to transport glucose into cells, inducing utilization of fatty acids for energy: hence the term ketoacidosis. In the United Kingdom, 15.7% of undiagnosed pediatric diabetes cases present as DKA.<sup>2</sup> This is potentially fatal, with a

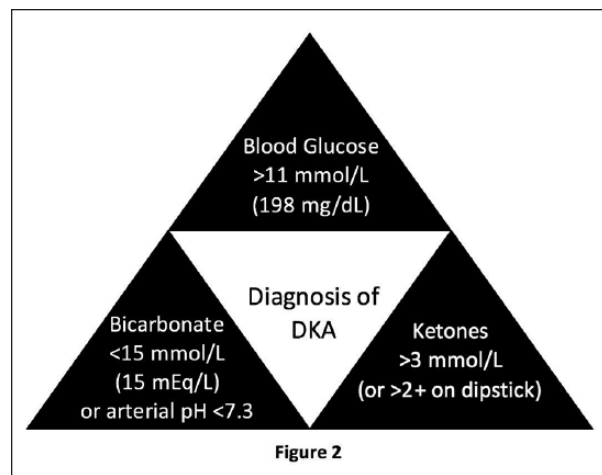
mortality rate of 2%<sup>3</sup>; this figure, however, is far greater with comorbid complications such as sepsis.<sup>4</sup> Unfortunately, almost all of these deaths are avoidable,<sup>5</sup> with retrospective identifiable failures in health care and/or patient identification. Regrettably, the failure of the GP in the presented case does not represent an isolated incident. Therefore, an assessment of this case is beneficial, assisting prevention of future errors.

There are 2 major reasons why the GP's primary diagnosis of pneumonia should have been questioned. The first of these is the considerably increased levels of thirst, and the second is a clear chest examination. With reference to the former, although benign in the majority of cases this should have been explored further by the GP on mentioning by the mother. Even with the presence of infective symptoms, the differential diagnosis should include DKA with reported polydipsia: 23.4% of DKA admissions are precipitated by an infective illness.<sup>3</sup> Further to this, a clear chest examination justifies an alternative diagnosis. The reason for these oversights is unclear; nonetheless, increased knowledge on the area would certainly be assistive. Any index of suspicion from the GP could have revealed the diagnosis, as investigations revealing 2 of the 3 diagnostic criteria for DKA are readily available in the community (see Figure 2).

As such, local and national educational initiatives on the recognition of DKA may be indicated. In addition to DKA, the reported patient was also a sufferer of trisomy 9p.

### Trisomy 9p and Diabetes

To the majority of medical professionals, trisomy 21, 18, and 13 are known as the only duplications compatible



**Figure 2.** DKA diagnostic criteria. Raised blood glucose and ketones are detectable within the community via BM pinprick and urinary dipstick, respectively. Data extracted from Savage et al.<sup>5</sup>

with life. However, the next leading chromosomal duplication syndrome is compatible with long-term survival; this is of the short arm of chromosome 9: trisomy 9p.<sup>6</sup>

Phenotypic manifestations of trisomy 9p are remarkably similar between individuals<sup>7</sup>; features include craniofacial malformation, developmental delay, and growth deficiency. Although the latter is due to dysfunction of the growth hormone/insulin-like growth factor-1 axis,<sup>8</sup> no other endocrinological dysfunctions have been reported in the syndrome. Hence, this is the first reported case of insulin-dependent diabetes mellitus in trisomy 9p. Although an association has never been suggested in the syndrome, there is considerable evidence implicating chromosome 9 in the formation of diabetes.

In recent times, novel susceptibility loci are being discovered for complex genetic traits such as diabetes through genome-wide association studies. These studies use a screening approach: DNA is taken from large cohorts of healthy and affected individuals and analyzed for significant differences. With this, there is an inherent flaw: the sheer number of tests performed generates a susceptibility to error. Although this can be limited by controlling false discovery rates,<sup>9</sup> conclusions are still limited in single studies. As such, meta-analyses of genome-wide association studies are necessary.

In 2011, one such study was conducted by Bradfield et al for 6 cohorts suffering from type 1 diabetes.<sup>10</sup> It identified a gene on the proximal arm of chromosome 9, GLIS3, as a susceptibility locus for type 1 diabetes. This confirms previous reports in *Nature Genetics*<sup>11</sup> and *Diabetes*.<sup>12</sup>

With the linkage of chromosome 9p to type 1 diabetes, this patient may provide unique insights on the molecular activity of GLIS3 in response to chromosomal duplication. Additionally, cases similar to this patient may remain unreported in the literature: this case may act as a prompt for other centers. If there is indeed an increased risk of diabetes in trisomy 9p, earlier identification of the reported patient's pathology could occur, avoiding fatal risks associated with late-stage DKA.

## Conclusions

The patient presented here is the first report of diabetes in trisomy 9p. With the implication of chromosome 9p in diabetes, this patient may provide unique insights into the genetics of diabetes. Moreover, if a correlation between trisomy 9p and diabetes exists, this may assist healthcare professionals in suspecting diabetes and its complications in these patients. Indeed, this report demonstrates the ease at which DKA is overlooked by healthcare services. As a potentially fatal but entirely preventable complication, early identification is essential. To aid this, educational initiatives are indicated.

## Author Contributions

SM: Contributed to conception and design; contributed to acquisition; drafted the manuscript; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

MR: Drafted the manuscript; gave final approval.

SS: Contributed to conception; acquired data.

SC: Contributed to conception; critically revised the manuscript; gave final approval.

## Declaration of Conflicting Interests

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