COCKAYNE'S SYNDROME - DIFFICULTIES WITH EARLY DIAGNOSIS

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ABSTRACT

The features of Cockayne's syndrome do not appear until 4 to 5 years of age. Early diagnosis is important for proper genetic counselling and antenatal screening. Despite various "diagnostic tests" offered by many authors, early diagnosis of the syndrome is still problematic. Four cases which were initially diagnosed as cerebral palsy are presented to illustrate this difficulty. Two cases were diagnosed as spastic cerebral palsy and the other two as familial spastic paraplegia. The features of Cockayne's syndrome appeared later.

Keywords: Cockayne's syndrome, genetic counselling, antenatal screening, cerebral palsy.

INTRODUCTION

When Cockayne (1) first described two siblings in 1936 with the clinical features of the syndrome that now bear his name, he characterised them with a triad comprising "Dwarfism with Retinal Atrophy and Deafness". These children were growing normally for the first two years and then started to develop features of cachexic dwarfism, mental retardation, delayed motor milestones, optic atrophy, retinitis pigmentosa, partial deafness and photodermatitis. A review paper on them ten years later, described the appearance of the facies now accepted as typical of Cockayne's syndrome ie. sunken eyes with loss of orbital fat, prominent nose and prognathism (2). Additional features include sexual infantilism, corneal opacities, cataracts, large hands and skeletal deformities (2).

Since Cockayne's reports, many similar cases have been reported and additional features eg. intracranial calcifications, osteoporosis, nystagmus, poor pupillary response to light and mydriatics, hand tremors, reduced sweating and lacrymation, carious teeth, hepatosplenomegaly and atherosclerosis have been added to this heterogenous syndrome (3-6). Not all cases of Cockayne's syndrome published completely fulfil the original criteria described by him and of interest especially, are some cases with very early onset of clinical features in infancy (7).

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Extensive work have also been done to elucidate a possible intracellular enzymatic defect in Cockayne's syndrome, in particular the hypersensitivity of cultured fibroblasts or lymphoblastoid cell lines of these patients to ultraviolet irradiation and the subsequent cellular DNA and RNA response (8-11). Attempts have been made to use this characteristic as a pathognomonic test for Cockayne's syndrome (10,12).

It is the purpose of this report to present four siblings who because of their presenting features of spasticity were presumed to have cerebral palsy until the typical features of Cockayne's syndrome appeared as well as to highlight the difficulty in diagnosing Cockayne's syndrome early, especially in children with unfavourable perinatal histories.

CASE REPORTS

Case 1

GKL (Fig 1), a Chinese boy, was born on 7 July 1978 from a non-consanguinous marriage by emergency Caesarian section after 31 weeks gestation for severe eclampsia of pregnancy. Birth weight was 1.5 kg and the child required ventilatory support at birth for Hyaline membrane disease. He remained in an incubator for 3 months. The first pregnancy for the mother ended in a still birth after 30 weeks gestation, also from severe pre-eclampsia.

His first recorded visit was at the age of two and a half years when he was referred for delayed milestones. Head control was achieved at 9 months, he rolled over at one year and could recognise his parents at 2 years old. He sat at 3 years old. When seen, he was microcephalic with increased tone and reflexes in the lower limbs. In view of his unfavourable perinatal history, a diagnosis of spastic diplegia was made.

The child never walked and his milestones subsequently regressed. He was admitted at the age of 6 for severe gastroenteritis and was found to be severely mentally retarded and bedridden. He was grossly cachexic with a weight of only 7 kg and occipital frontal circumference (OFC) of 39 cm. He tended to adopt a

"foetal" position. His cry was high pitched and tone and reflexes were markedly increased in all four limbs.

At 8 years old, he became thinner and more emaciated (weight 6.2 kg) with marked kyphosis. Scalp hair and eyebrows were sparse and ears were bat-like. Both eyes were sunken with a left corneal opacity and bilateral optic atrophy. He was deaf as well. Teeth were carious. Tone and reflexes in all limbs were increased. Both testes were undescended and the penis was infantile in size. It was at this stage when his features became obvious that a diagnosis of Cockayne's syndrome was made.

The child continued to regress and died at the age of 9 from a chest infection. At death he weighed only 5.2 kg.

Fig. 1
Case 1 (GKL at 8 years of age)

Case 2

GJS (Fig. 2), the younger brother of GKL, was born on 19 July 1981. Perinatal circumstances were remarkably similar to his brother's. He was also delivered after 31 weeks gestation by emergency Caesarian section for severe eclampsia of pregnancy. Birth weight was 1.6 kg and he developed respiratory distress syndrome with apnoec spells as well as Klebsiella septicaemia in the neonatal period. He required ventilatory support for a week.

His subsequent milestones were delayed. Head control was achieved at 8 months and he sat with support at one year. He could manage to speak a few monosyllables at one and a half years and stood for short periods with support at 17 months. At 2.5 years he was completely dependent for his feeding and toilet needs. At this time, physical examination revealed he was small for age with his percentiles less than 3rd % (weight 6.6 kg, length 69 cm, and OFC 42 cm). There were bilateral bat-like ears, increased tone and reflexes in the lower limbs and kyphosis. Again, in view of his unfavourable perinatal history, a diagnosis of spastic diplegia was made.

After 9 months old, he started to regress

developmentally. When admitted at 4 years old for a chest infection, he was found to be dwarfed and emaciated with a weight of only 4.5 kg. He could tripod-sit with difficulty. There were spasticity, hyper-reflexia and extensor plantars in the lower limbs. His eyes, vision and hearing were noted to be normal. There was marked pectus carinatum. Teeth were carious, testes undescended and genitalia infantile.

At 5, he could no longer sit with support. He was cachexic and eyes were sunken with bilateral cataracts. A diagnosis of Cockayne's syndrome was then made. At 6, he became bedridden and on one of his visits was noted to have cold and blue peripheries. He became kyphotic and contractures developed.

His hearing also deteriorated and he became deaf and blind at 7 years old. There were bilateral corneal opacities and cataracts. Both pupils were pin-point and did not react to light. His weight remained low at 4.6 kg.

He was subsequently admitted 11 times for recurrent chest infection and died at the age of 8 from bronchopneumonia.

Fig. 2
Case 2 (GJS at 6 years of age)

Case 3

MA (Fig.3), an Indian boy was born on 12 August 1973 from a consanguinous marriage, both parents being first cousins. This was a full term, uncomplicated delivery with a birth weight of 3 kg.

The child rolled over at 6 months, had a social smile at 8 months and sat up with support at one year. He could manage to speak a few monosyllables at 16 months. He was seen at the age of two for delay in walking. At that time he was noted to be dwarfed with a high arch palate, low hairline and bat-like ears. There was bilateral equinovarus deformity of the feet and examination of the central nervous system was normal. A diagnosis of delayed milestones of unknown cause,? syndrome was made by the attending doctor.

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He managed to walk with support at three years but his speech remained monosyllabic. His percentiles then were about 50th% (weight 11.6 kg, OFC 46 cm and length 99 cm). At 7, he could indicate his toilet needs but required help. He could not feed himself. His eyesight and hearing were normal. There was slight spasticity with hyper-reflexia of the lower limbs and he was diagnosed as spastic diplegia. He was subsequently seen at the Spastic Children's Association and re-referred back to us at the age of 13. The referring notes made mention to the fact that the child was "not eating well" and "seems to be shrinking". He was then no longer able to walk with support.

At 13, he was thin and cachexic with deepset eyes and prominent ears and nose. There were bilateral corneal opacities and the optic discs were pale. Dental caries were present and palate was high arched. Tone and reflexes were increased in the lower limbs. There were bilateral tendo-archilles contractures but the child could walk with a spastic gait. He had lost his monosyllabic speech and could only whine when upset. Testes were undescended and genitalia infantile.

A diagnosis of Cockayne's syndrome and familial spastic paraplegia was made at this time. At 15 years he became bedridden with joint contractures. Cataracts were noted in both eyes and both pupils were small and unresponsive to light. He was subsequently admitted a few times for poor feeding.

The child died in his sleep at the age of 15.

Fig. 3
Case 3 (MA at 14 years of age)

Case 4

HB (Fig. 4), an Indian girl, the younger sister of MA, was born on 26 March 1979 by full term, uncomplicated delivery with a birth weight of 3.3 kg. Like her brother, milestones were delayed from the beginning.

She had head control at 6 months, sat up at 8 months, stood with support at one year and walked with support at two years. She had monosyllabic speech of a few words at 18 months.

As her early development appears to parallel that of her elder brother, MA, her parents paid scant attention to her developmental delay. Her first recorded visit was at 4 years for speech delay. At 4, she could indicate her toilet needs and feed herself. At 5 years, she was thin, short and microcephalic, with a weight of 12 kg, length 95 cm and OFC 43 cm. She could not manage any intelligible speech. Tone and reflexes were increased in the lower limbs and she walked with a spastic gait. Eyes, ears and facial features were normal. In view of similar featues seen in her brother, the possibility of familial spastic paraplegia was entertained.

She managed to walk unsupported at 6 years old. At 8, she could no longer ambulate and could only stand with support. At this time she had features like those of her brother's and was thin and cachexic. Both eyes were sunken with bilateral corneal opacities and rotatory nystagmus. Pupils were pin-point and did not react to light. Both ears were large but hearing was normal. There were bad dental caries. Tone and reflexes were markedly increased in the lower limbs. A diagnosis of Cockayne's syndrome was made at this time.

The child is at present confined to a wheelchair and has also developed bilateral cataracts.

Fig. 4
Case 4 (HB at 8 years of age)

SUMMARY

The age of onset of the features of Cockayne's syndrome in the four cases presented is summarised in Table I

Table I

Comparison of age of onset of clinical features (in years).

Clinical Features	Case 1 GKL	Case 2 GJS	Case 3 MA	Case 4 HB
Microcephaly	2	4	3	5
Cachexic dwarfism	6	4	3	5
"Facies" of sunken eyes, large ears, prognathism & loss of facial adipose tissues	8	5	13	8
Carious teeth	8	4	13	8
Cataracts	8	5	15	9
Corneal opacities	8	7	13	8
Pin-point and unreactive pupils	-	7	15	8
Optic atrophy	8	7	-	-
Blindness	-	8	15	-
Deafness	8	7	-	-
Cold, blue extremities	-	6	13	-
Bedridden	never walked	6	15	wheel-chair at 8yrs
Delayed milestones	from birth	from birth	from birth	from birth

DISCUSSION

Cockayne's syndrome is a heterogenous syndrome with various authors citing different features in their cases (2-6). The consistent clinical features appear to be cachexic dwarfism with a typical prematurely senile facies of sunken eyes, loss of facial adipose tissue, thin nose and large ears, with microcephaly, sensorineural deafness, retinitis pigmentosa, optic atrophy, photosensitivity, ataxia, peripheral neuropathy and mental retardation. Developmental deterioration begins at about two years of age. Although most cases ultimately become bedridden and develop joint contractures; spasticity with increased tone, hyperreflexia and extensor plantars do not appear to be a common presenting feature. No mention of spasticity was made in Cockayne's (1,2) original cases. Neill and Dingwall's (3) two cases had brisk reflexes but plantars were flexor and limbs stiff but not spastic. In fact other authors have described a decrease in muscle tone and diminished deep tendon reflexes (5,6). Fujimoto (13) made mention of a case with clasp-knife spasticity of the extremities.

Our four cases presented with signs of spasticity especially in the lower limbs and were diagnosed and managed initially as for spastic diplegia. Two siblings (GKL and GJS) had suspicious perinatal histories which justified such a diagnosis but a similar justification is absent in the other two siblings (MA and HB). A sizeable number of cases described actually had delayed developmental milestones starting in infancy even before the onset of the characteristic features of Cockayne's syndrome (3,4,6,7,13). This feature is not consistent however (1,2,5,8,14).

The combination of early developmental delay with spasticity especially in those with suspicious perinatal histories can be misleading and may lead to a delay in correct diagnosis.

In our patients, GKL and GJS were born of non-consanguinous parents. They were both delivered by emergency Caesarian Section for maternal pre-eclampsia and had respiratory distress syndrome requiring ventilatory support for some days. This could have contributed to brain damage resulting in both having spastic diplegia and subsequent developmental delay. The occurrence of Cockayne's syndrome would most likely be a coincidental entity.

In the case of MA and his sister HB, they were offsprings of a consanguinous marriage. Both presented with delayed milestones and spastic diplegia. The regression of both physical and mental milestones occurred before features of Cockayne's syndrome appeared. Perhaps they had not only Cockayne's syndrome but familial spastic paraplegia as well.

It is of interest to note that GKS and GKL were markedly dwarfed and were more physically and mentally disabled then MA or HB. This could have been a result of their poor perinatal history. On the other hand, they could have been manifesting a much more severe variety of Cockayne's syndrome.

Diagnosis of Cockayne's syndrome is straight forward in those with all the classical features. Unfortunately, quite a number of years would have lapsed before these features became prominent.This would mean a delay in proper parental advice and genetic counselling. In our cases, the earliest onset of the facial features of Cockayne's syndrome occurred at 5 years, with one child occurring as late as 13 years old. Cockayne's (1,2) original cases were described and diagnosed when the children were 6 and 7 years old respectively. In fact most cases in the literature were diagnosed only in the second half of the first decade (3-6, 14).

With the feasibility of early and accurate antenatal diagnosis (8, 15-17), it can be appreciated that it is important to diagnose this condition as early as possible to enable early subsequent antenatal screening.

Routine investigations have been used in an attempt to elucidate a pathognomonic test for Cockayne's syndrome. Alton (18) analysed the radiographic changes in three patients and described "pathognomonic changes" in the vertebral bodies viz. coarsened trabeculae, flattening and notching of vertebral bodies and persistence of the nutrient canal. Similar changes have been described by other authors as well (13,19). Unfortunately these radiographic changes were described in patients whose clinical picture were already classical of Cockayne's syndrome and did not in anyway aid in early diagnosis. Levinson (20) suggested the use of CT scan to detect early calcification in the basal ganglion and felt that a diagnosis could be made as early as 3 years of age using this.

Landing (21) even suggested an anatomical study of the eccrine sweat glands which he found to be abnormally small for age in Cockayne's syndrome, as a possible

diagnostic tool.

The aetiology of Cockayne's syndrome remains unknown although some authors have suggested inborn errors of metabolism as a possibility. However, attempts to identify this nature have been unsuccessful to date (4,6,7). The association between Cockayne's syndrome, premature ageing , atherosclerosis and possible inborn error of lipid metabolism have been raised but detailed biochemical analysis of serum lipids, cholesterol, phospholipids and proteins have usually been normal (4,6,14). Occasional abnormal results are more exception than the rule. Lazzlo (22) described a patient with very low HDL- Cholesterol and Fujimoto (13) made reference to a patient with type II Hyperlipoproteinaemia which may be seen in some normal people as well.

Attempts to attribute the dwarfism seen in Cockayne's syndrome to growth hormone deficiency have also failed as there is a normal growth hormone response in these patients to i/v Arginine (13).

There are some similar features between Cockayne's syndrome and Leucodystrophies. Both present after an initial period of apparent normality with progressive disorder of the central nervous system; leading to mental retardation, blindness, deafness and death by inanition. Both may have cerebellar and extra-pyramidal signs of ataxia, nystagmus and tremors (14). This apparent similarity is further attested to by neuropathological findings of widespread patchy demyelination and neuronal loss in the central and peripheral nervous system of patients with Cockayne's syndrome (12,14,23-26).

Assays of white blood cell enzymes (Sphingomyelinase, galacto-cerebrosidase, galactosidase and Arylsufatase A) in Cockayne's syndrome have however been normal (7).

Peripheral neuropathy with segmental demyelination, remyelination and onion bulb formation of the sural nerve has been described earlier by Moosa (14). Subsequent detailed electron micrographic studies revealed presence of unusual membrane-bound granular material in the Schwann's cells and perineural cells (25). Grunnet (25) suggested the use of this feature to aid in the diagnosis of Cockayne's syndrome. As these changes, which are characteristic of granular cell myoblastoma (which may be seen in neurofibromatosis as well) have not been consistently described, it is doubtful whether peripheral nerve biopsy will become a useful tool in the early diagnosis of the syndrome (12). Furthermore, although the incidence of peripheral neuropathy has been quoted at 10-20% (25), it is unclear when the onset occurs. It is difficult to test for peripheral neuropathy in mentally retarded children and an accurate assessment of the sensory function is almost impossible. Grunnet's patient already had clinical evidence of neuropathy when nerve biopsy was done (25). It would be interesting to see if there are other earlier neuropathological changes which may herald the onset of peripheral neuropathy in these patients.

The discovery that fibroblast cultures derived from patients with Cockayne's syndrome exhibited an increased sensitivity to ultraviolet light but not X-irradiation suggested an enzymatic defect in the repair of UV-light induced DNA damage (8). This feature is also seen in cells of Xeroderma pigmentosa patients who although showed photosensitivity similar to Cockayne's syndrome, also exhibited a high incidence of sun-light induced skin cancer.

It is believed that such cancers are uncommon in Cockayne's syndrome because of their ability to excise UV light induced pyrimidine dimers with the same efficiency as normal cells (8).

It is tempting to link the premature ageing seen in Cockayne's syndrome with a lower capacity of its cells to perform unscheduled DNA synthesis after a report of such a finding in diploid cells of mammalian species with shorter life spans (9). Senescent normal cells in culture also exhibit a reduced capacity for unscheduled DNA synthesis after UV irradiation (9). Cockayne's syndrome cells have however been found to have normal levels of UV light induced unscheduled DNA synthesis (27).

Similarly, progeria cells have been shown to. be defective in the repair of single-stranded DNA breaks induced by ionising radiation (9). Although this has not been confirmed by others, (9) such a finding has also not been reported in Cockayne's syndrome cells (9,10,28,29,).

At present, the relationship between altered DNA repair and cell ageing invitro has not been unequivocal. The exact molecular repair defect in Cockayne's syndrome has yet to be clarified although suggestions that this defect may lie in a later step of excision repair, perhaps the final ligation process (29), have been offered but yet to be confirmed (28,29).

Suggestions to utilise the hypersensitivity of Cockayne's syndrome fibroblasts to UV light and UV-mimetic agents as a diagnostic test have been made (8, 12). Unfortunately some have demonstrated that this hypersensitivity is not such a consistent feature as previously thought (30). A similar suggestion to utilise this feature as a basis for antenatal diagnosis was made by Schmickel (8). Sugita et al (33) subsequently reported that amniotic fluid cells of Cockayne's syndrome patients were considerably more sensitive to UV light than normal amniotic fluid cells and skin fibroblasts from normal donors. Although he was successful, it took 5 weeks from amniocentesis to obtain a preliminary result and a further one week to confirm it. Hence this would necessitate amniocentesis very early in pregnancy for it to be useful as an antenatal test for Cockayne's syndrome.

In normal cells, DNA damaged by UV irradiation results in depression of both DNA and RNA synthesis which recovers soon if low UV doses are given (15). In Cockayne's syndrome cells, there is failure of this recovery to occur (31,32). Lehmann (15) made use of this differential response of RNA synthesis in normal and Cockayne's syndrome cells after UV irradiation as an antenatal test and obtained results within two to three weeks of amniocentesis.

At present it would appear that an absolute unequivocal diagnostic test for Cockayne's syndrome is far from near and most tests offered as diagnostic suffer from the limitation of having been tried on only a few patients. Until a good reliable test that has gained widespread acceptance appears, a keen sense of suspicion especially in those with regression of milestones and a family history of similar neurological disorder; together with close follow-up, is perhaps the best way to detect these cases early. It seems also that our future understanding of the molecular basis for normal ageing would lie in further research into premature ageing disorders like progeria and Cockayne's syndrome and perhaps herein lies the key to mankind's lifelong dream of immortality.

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