Neurological abnormalities in the 'cri-du-chat' syndrome¹

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SUMMARY An unusual case of the cri-du-chat syndrome is described in a 6½ year old boy, who, as well as attacks of stridor and choking, showed disorders of spatial perception and cerebellar signs in the form of nystagmus, clumsiness of the hands, and ataxia. Pyramidal signs were also present. He was only mildly retarded mentally. Psychological testing showed that he had a severe deficit for number processing, and also constructional apraxia. Surprisingly, his vocabulary was quite good, as was his reading capacity. Chromosome analysis showed a very small deletion of the short arm of the group B chromosome. In infancy this diagnosis may be suspected because of the high-pitched cry and attacks of stridor and choking. In late childhood, when the signs may be only of a neurological disorder, its recognition may be difficult without confirmation from chromosome studies. The neurological features of this disease are reviewed.

The cri-du-chat syndrome was first recognized by Lejeune, Lafourcade, Berger, Vialatte, Boeswillwald, Seringe, and Turpin (1963). Females are more prone to it than males, the relative incidence being about 2 to 1. About 100 cases have been described (Polani, 1969). Practically every patient has been noted to have an abnormal cry in infancy and this has been likened to the cry of a cat or kitten. It has also been described as sounding like a seagull in distress. As the child gets older the abnormal cry may be lost. One child when sneezing made a noise like a crow, and also suffered from hiccups (Turner, Bass, and Kaplan, 1966).

The following features are commonly found: microcephaly; gross mental retardation and motor retardation; physical retardation and failure to thrive; hypertelorism; epicanthic folds; downward slant to the palpebral fissures—anti-mongolism; strabismus, the incidence of this is very high indeed.

Less common features are the following: the corneae may be abnormally large—giving the

child a very alert appearance; premature greying of the hair; acyanotic heart disease.

The details of the neurological conditions found will be described in more detail below.

CASE REPORT

The proband was referred by his own doctor in 1969, at the age of 6½ years. He was the second of three children, the other two being normal. The father was normal. The mother was a nurse and was able to give a good account of his past history. The parents were unrelated. Detailed records were available from an early age.

When the mother was two months pregnant she had been exposed to German measles and had received gamma globulin. The delivery was normal at full term and the birth weight was 3.6 kg (7 lb 15 oz). At birth his mother noted that he had a triangular-shaped head. He was breast-fed for three weeks. When bottle feeding was started it was found to be difficult and he vomited occasionally. The vomit always contained much mucus. He always had a high-pitched cry. His father said his cry was like that of a Siamese cat. Weight gain was slow but steady.

His developmental milestones were a little delayed. He did not smile until he was 10 weeks old and he developed head control at 4 months. There was a

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history of a single bout of diarrhoea with passage of pale loose bulky stools.

He was examined at the age of 1 year when he was found to be fair-haired and blue-eyed. The skull was asymmetrical and head circumference was 40 cm ($17\frac{7}{8}$ in). He was able to sit momentarily. He was admitted to hospital at that age for 10 days and while there was found to be a happy child who often made odd clucking noises. He was a poor feeder but this was attributed to mental retardation. Limb movements at times appeared abnormal and were observed to be athetotic. His respirations were always noisy. He vomited occasionally and there was much mucus in the vomit. There was marked facial and skull asymmetry. The nasopharynx contained much watery mucus and over the upper respiratory tract transmitted noises could be heard. Radiographs of his chest showed an enlarged thymus gland.

At the age of 18 months he had stridor. He frequently choked over his food and had a hoarse cry. The neighbours had commented that he had a very

shrill cry and he cried like a cat. The difficulties with his feeding persisted.

A report on him at the age of 3 years stated that he often suffered from abdominal colic. He screamed constantly and took only small amounts of food. He did not sit up till the age of 16 months and he was nearly 2 years old before he stood up—but he walked soon after. At the age of $2\frac{1}{2}$ years he had started to speak. He was reported as being very fidgety when aged 3. Also he was easily upset and very tense. He was thought to have some nervous spasm of the bowel associated with excessive aerophagy. He did not give the impression of being very backward.

In his past history he had had measles, otitis media, and mumps. He had received triple vaccine, polio vaccination, and a booster injection. It had been noted that he had a lazy right eye.

At the age of $6\frac{1}{2}$ years the difficulties with his feeding had persisted and he still choked over his food. He was quite continent, was clean in his habits and had learned to dress himself. He was allergic to

FIG. 1. Frontal view of patient.

FIG. 2. Lateral view of patient.

wasp stings. The mother repeatedly mentioned that right from birth he had an odd cry and on one occasion used the words 'he sounded like a strangled cat'. His voice was husky and he still had a hoarse cry. He dropped objects that he was holding. His balance was poor and he dithered on stairs.

On examination at that age it was noted that he looked very alert (Figs 1 and 2). His voice was

husky. There was nystagmus when he looked to the right and he showed a slight squint. His arms were hypotonic and there was ataxia of the lower limbs and intention tremor of the left hand. The left plantar response was extensor. His handwriting was odd and he wrote his name in a curious pattern.

Mr. A. E. Howarth (consultant ENT surgeon) obtained the history that he often became cyanosed

FIG. 3. Chromosome pattern showing deletion of short arm of one chromosome, No. 5.

and choked over his food. There had been six attacks recently. He still had a cry like a cat occasionally at night. There was a history of repeated colds.

He was admitted for laryngoscopy and found to be somewhat wheezy. Under anaesthesia it was found that his epiglottis was normal. The larynx was apparently normal when paralysed with scoline but when he was recovering it was seen that there was asymmetry of the larynx, with the right arytenoid lying forward, and there was no movement of the right vocal cord. Oesophagoscopy was normal.

LABORATORY AND RADIOLOGICAL INVESTIGATION At the age of 1 year blood examination showed (two estimations) haemoglobin levels of 72% and 68%, with a normal total white cell and differential count (7,700/c. mm).

Urinary aminoacid pattern was thought to be at the upper limit of normal on one occasion, and on another occasion slightly raised levels of serine, glutamine, alanine, glycine, and histidine. Serum proteins were normal. His blood count showed 11.5 g haemoglobin/100 ml. with 10,000 white cells per c. mm and normal leucocytes and platelets. The sedimentation rate was 26 mm (Wintrobe). The serum glucose when fasting was normal (70 mg/100 ml.). The CSF protein was 48 mg/100 ml. with a slight increase of globulin but the specimen was slightly bloodstained. The CSF glucose was normal.

An EEG at the age of 1 year showed moderate asymmetry between the activities in the frontocentral regions but no definite paroxysmal features.

A pneumoencephalogram at the age of 6½ years showed good filling of all components of the ventricular system, which were normal in situation, but the left lateral ventricle showed slight rounding of the angle, indicating slight enlargement of the ventricle.

Chromosome studies were undertaken when this patient was aged 6½ years. Metaphases from a peripheral blood culture were examined and the number of chromosomes was found to be the normal 46. The sex chromosomes were XY, the normal male configuration. Very careful examination showed that there was an abnormality in group B: chromosomes nos. 4 and 5, Denver system. One of these showed a very small deletion of the short arms (Fig. 3). This was more obvious in some cells than others (Fig. 4). The chromosome preparations were sent to Dr. Jacobs at the Medical Research Council's Clinical and Population Cytogenetics Research Unit, Edinburgh, and she confirmed this finding. Her report reads, 'three independent observers all agree that he has a deleted group B chromosome (46XY, Bp-). However we all agree that the amount of deleted material is really very small'.

Chromosome pairs nos. 4 and 5 cannot be dis-

FIG. 4. Pairs of chromosomes. Numbers 4 and 5 show deletion of one chromosome, No. 5.

tinguished morphologically, but they can be differentiated by autoradiography using a radioactive DNA precursor. In this way it has been shown (Miller, Breg, Warburton, Miller, Firschein, and Hirschhorn, 1966) that patients with the cri-du-chat syndrome have a deletion of chromosome no. 5. There are a very few cases with a different and more severe spectrum of congenital abnormalities who also have a similar deletion. In some of these cases autoradiography has been carried out and the abnormal chromosome has been shown to be a no. 4 (Wolf, Reinwein, Porsch, Schröter, and Baitsch, 1965; Taylor, 1970). As this patient did not have the gross malformations described in cases of a deleted no. 4, and had a history of the 'cat-cry', the abnormal chromosome has been placed as a no. 5. It was not possible to examine his cells autoradiographically.

Some cases of cri-du-chat syndrome are known to be due to a familial balanced translocation (Lejeune, 1965; Laurent and Robert, 1966) in which case there is a risk of another abnormal child being born in the family. Therefore blood cultures from the patient's parents were examined. Both showed normal karyotypes; these findings were also confirmed by Dr. Jacobs.

PSYCHOLOGICAL STATUS He was assessed on several occasions between the ages of $6\frac{1}{2}$ and $7\frac{1}{2}$ years. As no information concerning specific difficulties was available to the two psychologists who assessed him, the initial assessments were 'blind'. Detailed psychometric studies of spatio-motor, cognitive, and language abilities were embarked upon, as his appearance and gait were so unusual. Assessments scores on the Wechsler Intelligence Scale (WISC), the English Picture Vocabulary Test, the Bender-Gestalt Visuo-Motor Test, the Frostig Developmental Tests of Visual Perception, and the Illinois Test of Psycholinguistic Abilities (ITPA), were done. They yielded a most unusual and interesting profile.

Intelligence It is usually misleading to quote a deviation intelligence quotient without qualification. He was initially reported by a local authority physician to show a Binet IQ of 91. About a year later, on the WISC, his scores were significantly lower than this (V IQ 75, P IQ 87: full scale score 78). Children showing signs of visuo-motor disturbance commonly manifest a large verbal performance discrepancy (Abercrombie, 1964; Langan, 1970) and, as his open-field language handling and vocabulary appeared to be quite sophisticated, the poor verbal score was rather surprising. There was a great deal of subtest scatter of 13 points on the full scale WISC and the very poor achievement in the arithmetic subtest pulled the verbal subscale down very considerably.

He had great difficulty in number processing and this is discussed later: on the two subtest scores with greatest discrimination however he scored at a near-average level. On the Performance Scale his poorest results were on the Block Design and Object Assembly items and may fairly be labelled as constructional apraxia. He was unable to attempt the simplest items on the Book Form of Raven's Coloured Progressive Matrices, becoming distressed and tearful when confronted with the first page.

Mathematics He showed both clinically and at school a particular incapacity to deal with number problems. A few *ad hoc* tests were carried out with the aid of materials available in the room (Fogelmann, 1970). A jug, water, and a few cups were used to test his ideas of 'conservation of quantity' but he firmly rejected this and treated attempts to change his mind about it with some hilarity. This would suggest that his conceptual development is as yet at Piaget's first stage.

Cuisenaire rods were used in an attempt to see whether he was able to size-order a series but he was quite unable to do this, even when a model was placed before him and helpful suggestions were made. He had a rudimentary schema of seriation for he usually managed to arrange the rods so that seriation was complete for each group of three, another series being commenced once he had placed three rods in serial order. His mathematical notions were at the level of a 5 to 6 year old child and it was considered that his difficulties in mathematics would repay further studies at a later age.

Visual perception and motor control When first examined at the age of $6\frac{1}{2}$ years (September, 1969) he was asked to complete the Bender-Gestalt Visuo-Motor Test (Fig. 5). It proved quite impossible to score the drawings; indeed, it was very difficult to identify each protocol with the original model (Fig. 6).

The Bender-Gestalt Test, although affected by both receptive and expressive disorders, fails to distinguish usefully between them: on a second occasion, therefore, he was asked to trace the drawings as they are reproduced in Zazzo (1960) (Fig. 7). This time his drawings, although poor, were of a far higher quality. This suggests that his main difficulty was in holding a short-term visual memory trace.

The Marianne Frostig Developmental Test confirmed the suggestion that his difficulties were receptive rather than expressive: his hand-eye coordination was shown to be poor, but major disabilities were observed in the Scale subtests which purport to assess receptive rather than expressive functions.

FIG. 5. Bender Gestalt Visuo-Motor Test (after Zazzo, 1960).

Illinois Test of Psycholinguistic Abilities This patient was assessed on the ITPA in September 1970—the final testing of the series. He was then aged 7 years 6 months. The norms provided by Kirk, McCarthy, and Kirk (1968) suggest that his mean score was 1.3 standard deviation below the population mean: this is roughly the kind of result which would be consonant with a global IQ of 80 on a standard cognitive test with a mean of 100 and standard deviation of 15. This is very close indeed to the WISC full scale score of 78 obtained a year earlier and probably represents the level of intelligence he is able to mobilize at present. The pattern of his subtest scores was of considerable interest; when rank-ordered, from highest to lowest, they ran as follows:

Auditory reception	43
Auditory memory	38
Grammatic closure	37
Auditory association	34
(manual expression)	
Verbal expression	26
Visual reception	26
Visual memory	24
Visual association	22
Visual closure	20
Normal score = 40

FIG. 6. Copy of Fig. 5 by patient.

FIG. 7. Tracing of Fig. 5 by patient.

This confirmed the earlier impression that tasks concerned with verbal behaviour were handled much better than those concerned with visual material. The four visual tests had a mean standard score of 23—just over two standard deviations below the population mean and roughly equivalent to a WISC score of 68. This was about the same as the general 'perceptual quotient' obtained a year earlier on the Frostig Test. The five explicit language tests had a mean standard score of 35.6, which was very close to the population mean and equivalent to a WISC score of IQ 94. It may be concluded that this patient was most severely handicapped in the visual modality—and within that modality, in the receptive sphere—but that he was near the average in the understanding and use of language. It is true that his earlier WISC verbal score suggested that his verbal abilities were quite significantly lower than this; but his specifically poor arithmetic test results contributed to this low figure and the other subtests on which he did poorly (information and comprehension) appeared to measure, at that stage, general know-how rather than verbal ability *per se*.

It should be noted that despite these perceptual handicaps this patient was now reading fluently.

If we accept that there is a sharp bifurcation between levels of functioning it is also interesting to note that within each modality the rank order of subtests was roughly similar. In the auditory-grammatic subtests the order was: Reception, Memory, Closure, Association, Expression; in the visual subtests it was: Reception, Memory, Association, Closure (Manual expression does not clearly belong to either domain). In terms of Osgood's model (1963) the pattern is suggestive, although of course for a single case it cannot reach statistical significance.

Educational prognosis It should be noted that this patient had made reasonably good progress in writing and reading skills despite *prima facie* evidence of perceptual handicaps, and the earlier suggestions (McCracken and Gordon, 1965) that 'severe subnormality' was a usual concomitant of this condition—the cri-du-chat syndrome. Certainly cognitive and perceptual handicaps were present, yet in spite of this the patient was holding his own in a class in a normal state school designed for children of low general ability. His vocabulary, reading, and general language handling were not good, but they were considerably better than for many so-called 'normal' children.

DISCUSSION

Polani (1969) refers to the incidence of this condition as being between 1 in 50,000 to 1 in

100,000, or even less, live births. The oldest case described, aged 33 years, is that of Berg, Delhanty, Faunch, and Ridler (1965). Miller, Warburton, and Breg (1969) referred to 13 cases over the age of 12 and to one aged 55 years (in course of publication).

In a series of 55 cases reviewed by McGavin, Cant, Ferguson Smith, and Ellis (1967) 39 had the typical cri-du-chat. In another series of 18 cases reviewed by Berg *et al.* (1965) 16 had the typical cri-du-chat and one was doubtful. Attention has been drawn to the fact that in older patients the cri-du-chat may be absent (Ricci, Ventimiglia, Dallapiccola, Franceschini, and Preto (1965), and this may make the diagnosis very difficult if not impossible on clinical grounds in older children or adults.

Some authors have not found any abnormality in the larynx, but a leading article in the *Lancet* (1965) mentioned a soft mobile epiglottis and underdevelopment of the larynx as being responsible for the cri-du-chat. Zellweger (1966) described indrawing of the arytenoids and the epiglottis. Structural changes in the larynx or sublaryngeal zone were described in De Grouchy, Arthus, Salmon, Lamy, and Thieffry (1964) and Lejeune, Lafourcade, De Grouchy, Berger, Gautier, Salmon, and Turpin (1964a) and other authors.

The case described in this paper showed no structural changes but had paralysis of one vocal cord. The attacks of choking, which are very common, and also the high-pitched cry, suggest that there is a neurological abnormality of laryngeal function. It would appear that there is probably some neuromuscular incoordination in the act of swallowing which causes choking, and it is considered more than probable that a similar incoordination is responsible for the cri-du-chat in many of these patients.

Regarding the neuropathological changes, there are very few post mortem descriptions. Solitare (1967) described a 19 year old girl who died with this condition and he considered that she had a miniature brain but that its cytoarchitecture was normal. This is a concept which seems very much open to question and it seems that further work is required on this.

Lejeune, Gautier, Lafourcade, Berger, and Turpin (1964a) found a left cerebellar hemisphere that was smaller than its fellow. Crome and Stern

(1967) in their case described absence of the olfactory nerves with small optic nerves and optic chiasm. The central parts of the olfactory brain were absent and there was arrhinencephaly.

Clinically most of the patients show hypotonia of the limbs. A small number of cases have manifested spasticity. This was recorded by Milunsky and Chitham (1966). Dumars, Gaskill, and Kitzmiller (1964) described a child with spastic quadriplegia. A spastic shuffling gait occurred in the patient recorded by Bergman, Flodstrom, and Ånsén (1965). Spasm of the thigh adductors was found by McGavin *et al.* (1967). Of 18 cases reviewed by Berg *et al.* (1965) 12 were hypotonic and two were spastic.

Laurent and Robert (1966) collected three brothers with this condition, which was unusual as being prevalent in one particular family, and they all had extensor plantar reflexes and brisk tendon reflexes. De Grouchy *et al.* (1964) and Hustinx and Wijffels (1965) described extensor plantar responses also. Our patient showed a unilateral extensor plantar response.

In the series of 50 cases reviewed by McGavin *et al.* (1967) five had convulsions. Solitare's (1967) patient had convulsions until the age of 4 years. Hirschhorn, Cooper, and Firschein (1965) described a patient who showed as many as 20 myoclonic seizures a day and who subsequently died in a seizure. One of the patients recorded by Lejeune *et al.* (1964b) developed coma and hemiplegia as a result of complications due to congenital heart disease. Petit mal was present in a patient described by De Capoa, Warburton, Breg, Miller, and Miller (1967).

Tremors or tremulousness have been described by Turner *et al.* (1966) and Cavalieri, Mastella, and Tiepolo (1964). Laurent and Robert (1966) referred to one patient who not only had jerkiness of arm movements but synkinesia of the upper limbs. It is considered that the hypotonia shown by most patients could be of cerebellar origin and the cerebellar signs shown by our patient would also fit into this category. Berg *et al.* (1965) described a waddling gait. Unilateral optic atrophy was present in a case recorded by Lejeune *et al.* (1964b).

Air studies have only been carried out in a few cases. Dilatation of the lateral ventricles was found by Lejeune *et al.* (1964b) and Hustinx and Wijffels (1965). Wolf, Reinwein, Porsch, Schrö-

ter, and Baitsch (1965) had a patient who also showed nystagmus—Hirschhorn *et al.* (1965) also found absence of the septum pellucidum. The child described by Cavalieri *et al.* (1964) showed pachygyria.

Clinically, there is a great variation in the severity of the physical abnormalities and the degree of mental retardation. The karyotypes also show differences in the amount of chromosome material deleted. It is tempting, in view of the small deletion and the mildness of the abnormality present, to try and relate the size of the deletion to the degree of abnormality. But it must be remembered that different segments of the chromosome may be lost in each case.

As no abnormality could be detected in the parents of the proband this chromosomal deletion arose either during gametogenesis in one parent or in the very early zygote. It is generally accepted that terminal deletions do not occur in man, so that it is necessary to postulate two breaks and rejoining of the chromosome with loss of the interstitial part. Therefore, it is not possible to know which part of the chromosome has been lost.

The value of chromosome studies in such patients is twofold. They show a cause for the abnormalities so that other investigations into the reasons for the mental retardation need not be undertaken; and, if the karyotype of the parents is normal, they can be given a good prognosis for future pregnancies.

Although the disease is rare, the literature cited indicates that a number of the children born with this condition survive childhood and that they may be seen by neurologists dealing with young adults. It is hoped that the detailed description of this case may enable other similar patients to be recognized.

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