Benign (non-paroxysmal) familial chorea. Paediatric perspectives

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SUMMARY We describe a non-progressive choreo-athetoid disorder of early onset, present in three families. There were no appreciable abnormalities in pregnancy, during the perinatal period, or in infancy. In each case the family history suggested transmission as an autosomal dominant trait, the gene showing diminished penetrance. Other families have been reported with the disorder and such titles as benign familial chorea, familial essential (benign) chorea, or hereditary non-progressive chorea of early onset have been given to it. Our experience suggests that this is not a rare disorder, and that it is one likely to present in the paediatric age group; correct diagnosis is important so that unnecessary investigations are not undertaken, genetic counselling can be given, and proper management advice offered to families and schools.

We wish to draw attention to a condition little known to paediatricians, the symptoms of which appear in early childhood, possibly in the first year of life, invariably within the first decade.

Last year three families with this disorder were seen in Oxford and one child (Family 3, III, 3) is the youngest affected person to be described in detail.

In all families there was considerable anxiety about the cause of the problems. In two families the affected parent in each had been told that the condition could not be transmitted, and had undergone an extensive time in hospital and been subjected to unpleasant investigations and various forms of treatment, none of which had substantially modified the condition or clarified the aetiology. Both parents, understandably, did not wish their children to go through similar ordeals.

The disorder is not severely incapacitating and is non-progressive. However, problems do arise during childhood and these can be alleviated if the condition is understood; initially there is delay in motor development and often a tendency to fall frequently; learning and behavioural problems may become evident in school.

Case reports

Family 1 (Fig. 1). The early history and development of this boy (III, 3) had been normal, but he could not sit unsupported until 10-11 months, and he never crawled but dragged himself forward in a

Fig. 1 Pedigree Family 1.

prone position from age 8-9 months; he pulled to standing at 1 year but did not walk alone until after his second birthday. Delay in walking prompted referral to a paediatrician at 23 months. There was then a suspicion of athetosis but the involuntary movements gradually became more evident; at 5 years the diagnosis was athetoid cerebral palsy.

At 5½ years, when referred for assessment, his primary schoolteacher reported that any recorded work was poor and he was not allowed to take part in physical education 'because he is so unstable . . . he would need my whole attention.'

On examination he was an attractive child with good concentration but with motor abnormalities. Muscle tone fluctuated and power was poorly

sustained although it was initially normal. Gait was 'athetoid' and frequent brief choreiform movements of head, trunk, and limbs were evident particularly during skilled activities. There was no tremor, no nystagmus, and no speech disorder. Sensation, including vision and hearing, was normal. Tendon reflexes were normal (brisk) and plantar responses flexor. Intelligence was above average (WISC IQ 108).

One sister (III, 2) is mildly affected. At 5 years her gait had been bad: she is now a thin, fidgety 10-year-old child. Chorea is seen on skilled activity and she has only recently learned to ride a bicycle, but writing and physical education are acceptable.

The mother (II, 2) had had severe problems as a child. She had been diagnosed as having cerebral palsy, was extensively investigated and treated with physiotherapy and calipers; she had attended a special school. She had not been able to walk without calipers until 12 years old. She still has an athetoid gait and controls her jerks by holding her hands firmly and crossing her legs on sitting. The jerking is obvious when she eats. She is unable to carry a full cup of liquid, she drops things and is therefore nervous about carrying the baby.

Her parents are both dead and no similar problems have been reported among her 5 siblings and their children; these relatives have not been personally examined.

Family 2 (Fig. 2). This child (Fig. 2, III, 7) was referred aged 9½ years. Early history had been normal but she did not walk alone until 2½ years, and she fell frequently. For a while 'intoeing' was suggested as the cause of her falling and she saw an orthopaedic surgeon. She had never learned to skip or to run any distance, and still cannot easily pour liquids or carry full containers. Her peers tease her by calling her *Winnie Wobbles*.

Examinations showed a cheerful child, her legs bruised and scarred from falls. The choreiform movements and unusual features of muscle tone and power (found in Family 1, III, 3) were present.

Fig. 2 Pedigree Family 2 (see key in Fig. 1).

She had a fluctuating grip, slight intention tremor, dinner-fork posture of outstretched hands with piano-playing of the fingers. Writing was slow with a very tight grip. Neurological examination was otherwise normal. General intelligence was mildly retarded (WISC IQ 73); some other members of her mother's family were retarded but without chorea. There was some evidence of sensitivity and lack of self-confidence.

Her youngest sister (III, 9) is mildly affected with similar choreiform movements and posturing of the hands; skilled manipulation is unsteady and she finds it difficult to carry a full cup, which accentuates the abnormality of gait. The mother (II, 8) is normal but the father (II, 4) could not be examined.

A paternal 1st-cousin (III, 13) had had delayed and unusual motor development; he had sat unsupported at one year but had never crawled; instead he had dragged himself forward in a prone position from 8-9 months; he had pulled to stand and cruised at 14 months but could not walk unaided until 26 months and then he fell frequently. At 2½ years his gait was described as 'athetoid', he could not run without falling, had difficulty getting up, but did not use the Gowers's manoeuvre. Medical opinion had been sought but no diagnosis made, normal results were reported from serum creatine phosphokinase levels, skull x-ray film, electroencephalogram, and myelogram.

At 5½ years he still often fell, had difficulty climbing stairs, and could not run, jump, or hop. Nor could he kick a moving ball, although he could catch and throw. Examination showed generalised chorea, rather immature and slightly dysarthric speech, awkward wobbly gait with a tendency for his legs to give way suddenly especially on turning; he could stand on one leg for only 2 or 3 seconds. The rest of the neurological examination was similar to that of his cousin. He pressed hard when writing and the sides of a square were irregular because he jerked.

Two other paternal relatives (II, 7 and III, 1) have symptoms that suggest they have the disorder but so far neither has been personally examined. The grandfather (I, 2) is dead and the grandmother (I, 3) is thought to be normal; we have little information about the previous generation.

Family 3 (Fig. 3). This 15-month-old boy (III, 3) is the first child of a man who himself has a movement disorder. Pregnancy, birth, and infancy were uneventful, social milestones were passed normally although babbling was delayed until he was nearly 1-year old. He rolled at 5-6 months but dragged himself forward in a prone position from 9-10

Fig. 3 *Pedigree Family 3 (see key in Fig. 1).*

months, never crawling; he sat alone at 10–11 months and cruised jerkily at one year.

Examination showed a responsive normal-looking child, but there was excessive drooling, brief generalised choreiform movements were present at rest, and excitement or stress provoked larger amplitude athetosis. Reach was dysmetric with athetoid posturing and mature pincer grip was lacking. He was not able to get from lying to sitting or standing unaided and did not crawl but occasionally he would make two or three hesitant steps towards an adult. He was slightly hypotonic but examination was otherwise normal.

The father (II, 2) had had a movement disorder since early childhood and suffered from the many hospital admissions that ensued (for the purposes of observation and investigation) between ages 18 months and 12 years. As well as extensive biochemical tests on blood and urine he had had a lumbar puncture, skull x-ray films, electromyograms, several electroencephalograms, bilateral carotid angiograms, and chromosome analysis: all were reported as normal. Table 1 shows the diagnoses resulting from these admissions and the treatments prescribed. The frequent hospital admissions had disrupted his schooling and he did not do well; possibly slowness and untidiness in writing also contributed to his poor achievement. There had been no deterioration since early childhood.

He was seen in Oxford at age 29 years, by which time he had a quite good job in the Civil Service. He described himself as nervous, and a worrier. Involuntary movements would worsen if he was tired or stressed and, especially on waking, his limbs would thrash about. He could not carry a pint of beer without spilling it, nor could he do home decorating since his lines were crooked.

On examination he was restless and fidgety with brief choreiform movements of fingers, arms, and legs. There was a fine tremor with arms extended and on skilled tasks; writing was slow, he pressed hard,

Table 1 *Suggested diagnoses and treatments (Family 3, II, Case 2)*

Diagnosis	Treatment
Petit mal epilepsy	Primidone
Ataxic cerebral palsy	Physiotherapy
Epilepsy	Phenytoin and phenobarbitone
Familial periodic paralysis (no biochemical evidence)	—
Paramyoclonus multiplex	Benzhexol hydrochloride
Striatal epilepsy	Phenobarbitone
Paroxysmal choreo-athetosis	—
Functional ataxia (psychosomatic)	Psychotherapy
	Prochlorperazine mesylate

and had poor form-copying ability. His grip was fluctuant. He tended to stutter, with dysrhythmic speech; he could not protrude his tongue steadily, nor move it well from side to side. His gait was odd and clumsy and he could not stand on one leg for more than 20 to 25 seconds. In general the musculature was 'stiff' but there was no other clear abnormality.

The father's aunt (I, 8) is said to be a nervous and slightly twitchy person; his brother (II, 1) has prospered in business and is apparently free of the disorder, as are the father's parents and other close relatives.

Previously reported cases have been extensively investigated (Table 2) and no specific abnormality been found; some members of the families referred to us had also had investigations. Therefore, in the later families, further investigations were kept to a minimum. Serum caeruloplasmin and immunoglobulin levels were normal in II, 3 of Family 1, and in III, 7 of Family 2, and a computerised tomography (CT) scan was normal in II, 2 of Family 3.

Table 2 *Investigations carried out in previously reported cases for which no abnormalities were found*

Full blood count and film for acanthocytes, erythrocyte sedimentation rate	} Many
Full biochemical screen	
Karyotype	
Serum caeruloplasmin (n=3), protein-bound iodine (n=4), uric acid (n=5), Wassermann reaction (n=2)	
Routine urine analysis, amino-acid chromatography, and mucopolysaccharide screen—Many	
Cerebrospinal fluid routine analysis (n=2)	
Electroencephalogram (n=12)	
Skull x-ray (n=14), computer tomography scan of head (n=3), pneumoencephalogram (n=2)	

Discussion

Introduction and differential diagnosis. In 1967 two independent publications in the USA reported a new familial non-progressive choreiform disorder.^{1,2} Since then a few further such families have been reported.^{3-8,19} Most reports suggest autosomal dominant transmission. Damasio *et al.*⁹ described a non-progressive chorea of early onset associated with pronounced hypotonia and congenital nerve deafness in 2 of 4 siblings, the parents being normal; this probably represents a distinct syndrome, perhaps with autosomal recessive determination. Refsum and Sjaastad¹⁰ may have described a different disorder; there is insufficient clinical detail to distinguish their case from familial myoclonus (paramyoclonus multiplex).

The papers of Bird *et al.*,⁶ and of Harper,⁸ gave good reviews and described the differential diagnosis; these aspects will not be discussed in detail here. The distinction from Huntington's chorea is of particular importance. Huntington's chorea seldom presents in childhood and, in the few cases where it has done, early development was normal; gait was characteristically rigid and chorea less prominent. Rapid progression is the rule, accompanied by arrest in cognitive development and early death. Relatives with adult onset of Huntington's chorea can generally be identified and these, together with the affected children, may show evidence of caudate nucleus atrophy on CT scan, air encephalogram, or at necropsy. Table 3 summarises the differential diagnosis of childhood chorea.

Our patients have the features reported in other papers,^{1-8,19} succinctly described as benign familial chorea, although perhaps more clearly as familial non-progressive chorea or choreo-athetosis of early onset. The essential features are found in the history and examination (Table 4); so far no special investigations have proved useful and the underlying abnormality is not known.

Incidence. Bird *et al.*⁶ and Harper⁸ both discussed prevalence and this is difficult to estimate with so few case reports, . . . 'but is undoubtedly greater than the few reported cases suggest.'⁶ Our experience of three families referred within a year supports this view. It is a condition presenting in the paediatric age group but hitherto largely unrecognised in the UK. There is also the danger of overdiagnosis. If the diagnosis is made or suspected, one should seek for the condition among the close relatives. It should be differentiated from the other conditions listed in Table 3.

Genetics. Almost all reported pedigrees suggest autosomal dominant inheritance. In the early reports

Table 3 *Differential diagnosis of childhood choreo-athetosis*

Perinatal problems	Cerebral palsy
History of preceding illness	Sydenham's chorea (generally rheumatic fever). Other infections or encephalitides
Drug induced	Many, especially phenothiazines, phenytoin, and diazepam
Progressive disorders	Huntington's chorea ¹² AD Ataxia telangiectasia AR Juvenile cerebral gangliosidosis AR Lesch-Nyhan syndrome XLR Wilson's disease AR Neurological disorder with acanthocytosis AR(?) Familial calcification of the basal ganglia (normally of adult onset) AD Hereditary essential tremor AD Paramyoclonus multiplex (familial myoclonus) ^{13,14} mildly progressive, often asymmetric AD
Paroxysmal conditions	Paroxysmal kinesigenic choreo-athetosis ^{15,16} Movement-induced reflex epilepsy ¹⁶ Familial paroxysmal choreo-athetosis ^{17,18} AD
Non-progressive, non-paroxysmal	Benign familial chorea AD (AR?) Benign familial chorea with hypotonia and deafness ⁹ AR(?)

AD = autosomal dominant, AR = autosomal recessive, XLR = X-linked recessive.

there were few examples of male-to-male transmission, suggesting X-linked dominant inheritance as an alternative, but a later paper⁷ and our family 3 provide further examples of male-to-male transmission, which excludes X-linkage.

Inheritance in the family described by Nutting *et al.*³ is compatible with either an autosomal dominant or autosomal recessive gene; limitation of a dominant disorder to a single sibship may result from failure of penetrance in a parent, or failure to examine such parents.

Harper⁸ suggested that penetrance of the gene is nearly 100% in males (nearly all 'carriers' are symptomatic), while in females it is reduced to about 75%. In the very large pedigree of Burns *et al.*⁷ at least 2 unaffected but obligate male carriers, and 1 obligate female carrier transmit. In our Family 2

Table 4 *Essential features of benign familial chorea*

- (1) Choreic or choreo-athetoid symmetrical movements affecting limbs, head, and trunk
- (2) Early onset: all within first decade, many in first and second year of life
- (3) Chorea continuous (not paroxysmal) but fluctuating, aggravated by stress and fatigue, stops during sleep
- (4) Non-progressive, same intensity, or slight improvement from childhood into 5th, 6th, and 7th decades
- (5) Delay in gross and fine motor development (unless only slightly affected)
- (6) Apart from choreo-athetosis (and sometimes slight intention tremor) no abnormal neurological signs, no other systemic abnormality, no congenital stigmata. Investigations unhelpful. No structural abnormality of the central nervous system found
- (7) Intellect not affected
- (8) Familial incidence, probably autosomal dominant with reduced penetrance
- (9) No history of illness, drugs, birth asphyxia, jaundice, or trauma sufficient to account for the symptoms

there is transmission through one obligate carrier male (II, 4) who may be unaffected. Failure to trace the disorder back through many generations is most likely due to amelioration and concealment of symptoms with increasing age or failure to examine antecedents, rather than to a high mutation rate for what is usually a moderately benign disorder.

Clinical features and prognosis. In addition to the features listed in Table 4, some families have a mild intention tremor² (present in our Families 2 and 3). In some there is delay in speech development⁴ and later dysarthria⁴ or irregular speech rhythm⁸ (present in our Family 3) but ataxia and nystagmus have not been reported. Muscle tone is generally unaltered but occasionally it is slightly increased or slightly decreased⁷ (present in our Family 3) and grip is fluctuant (milking).^{2 4 5} Deep tendon reflexes are generally normal although knee-jerks may be pendulous (hung-up).^{1 4 5} Frequent falling is a common childhood symptom^{1 5 8} (present in our Family 2); it may be the presenting complaint. Gait is often described as wide-based, unsteady, and clumsy.^{4-6 8}

The clinical spectrum varies a good deal between and within individual families. Some people are very mildly affected without functional disability; among the family reported by Haerer *et al.*¹ were some mildly affected members who were not recognised as such by those with the disorder but who could be picked out by non-affected members. Such people are often described as restless, fidgety, and nervous.

General intelligence is normal. There have been a few reported cases with IQs in the 70s; these were

felt to be related more to family pattern and socioeconomic status than to the disorder.¹ There are a number of reports of greater than average intelligence.^{2 7 8}

The prognosis is good; most affected adults have brought up families and men are reported in fulltime work—such as electricians, air-line pilots, unskilled labourers. Life expectancy does not appear reduced. There is no deterioration, but rather a slight improvement in performance from childhood to adult life, affected people gaining some measure of control over their involuntary movements.

Mechanism of symptoms. The symptoms relate to the various components of the choreo-athetoid disorder. There are random fluctuations in muscle tone, not easily anticipated or counteracted, resulting in the fluctuating grip and difficulty with joint stability. Thus in early development there is motor delay, particularly in crawling, probably reflecting instability in shoulder and hip girdles; preferred ways of moving are rolling and dragging forward in a prone position. Once the child can walk independently, almost always delayed to 2 years or more, there is a tendency to fall suddenly.

The involuntary movements may continue to affect balance leading to the clumsy, wide-based gait and poor ability to stand on one leg, or to hop, skip, go up steps, run etc.

Hand function is affected too as described in the case reports; writing problems were mentioned by Sadjadpour and Amato.⁵ The hard grip, like the very controlled sitting posture, is an apparently effective attempt to prevent the jerks; Haerer *et al.*¹ also commented on this.

Main problems. These relate more to the handling of the situation than to the symptoms of the condition itself. Many affected children have undergone a prolonged time in hospital and been subjected to unpleasant investigations and treatment; this had been the case with both adults we examined, and Bird *et al.*⁶ described one man who had had two separate 1-year admissions as a child.

Attempts at treatment have been neither effective nor necessarily harmless—for example, prolonged psychotherapy, the encumbrance of calipers, and a variety of drugs including phenobarbitone, phenytoin, benzodiazepines, phenothiazines, reserpine, benzhexol; Harper⁸ mentioned a man who had his toes amputated to help him walk.

Some children have suffered teasing which has produced the secondary effects of anxiety, stammering, behavioural disturbances, lack of self-confidence, and increased sensitivity resulting in under-achievement (added to similar sequelae

which may result, iatrogenically, from too much time in hospital). The restlessness and fidgetiness has occasionally led to expulsion from school.

Management. Discussion of the diagnosis and prognosis is likely to alleviate parental anxiety. Informed genetic counselling is also important for the index family and close relatives. Hospital admission and extensive investigation can be avoided. Parents with affected infants may need help and guidance and, depending on the main problems, advice from a physiotherapist, occupational therapist, or speech therapist may be useful.

School staff will be greatly helped by an explanation of the child's particular difficulties and by understanding that fidgeting is involuntary. The principles of management of a child with a movement disorder and normal intelligence are well known to paediatricians and therapists with an interest in developmental problems but it may be necessary to explain these to their educational colleagues. If a child is to remain at a normal school, which should be the aim (Warnock¹¹), a teacher's assistant may be required to help both in the classroom and for physical education sessions. A strong medical recommendation may be needed.

Conclusion

It is believed that benign familial chorea is a fairly clear clinical entity. Diagnosis is important for family counselling, to prevent unnecessary hospital admission and investigation, and for appropriate recommendations to be made regarding management. In the past, children with this condition have suffered from behavioural disorders and learning problems at school, often resulting in underachievement; it is suggested that these can largely be prevented through a better understanding of the condition by those responsible for the child's management and education.

Addendum

In Family 2, III 2 has been examined and shows clear signs of being affected. We have obtained the hospital notes of II 2, which describe a choreo-athetoid disorder of unknown aetiology. In Family 3, II 1 and III 4 have been examined and are unaffected.

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