The past decade has seen unparalleled advances in the application of molecular genetic methods to the study of neurodevelopmental disorder, including disorders with significant learning disability. Alongside this development there has been a substantial growth in the number of studies attempting to link genomic changes (deletion, reduplication, or silencing of genes) to cognitive and behaviour outcomes: in essence to link genotype to phenotype. A main benefit of this approach is that it permits an insight into the range of strengths and difficulties that can be associated with a disorder which in turn can guide the general management of children and adults with genetic causes of learning disabilities. One such disorder that has attracted attention in recent years is Cri du chat syndrome (CDC), first described by the French paediatrician Lejeune in 1963 who coined the term ‘cri du chat’ (‘cry of the cat’). Indeed, the hallmark cat cry is still regarded as an important early clinical diagnostic feature of this syndrome in some but not all affected newborn infants. Further research in the 1960s and 70s resulted in the publication of numerous case reports and a triad of clinical features became associated with CDC: the cat-like cry, dysmorphic facies, and profound global learning disability. It is now recognized that this triad does not present in all patients. Additional clinical features were also cited as being significantly over-represented in the condition. These included increased early childhood morbidity, restrictive language skills, and severely delayed psychomotor development. This somewhat pessimistic portrayal of CDC was challenged in the 1980s by the findings obtained from population-based studies and questioned more intensely in the 1990s as advances in molecular genetics allowed greater clarification of the syndrome’s genotype and more detailed cognitive and behavioural studies demonstrated wider variability within the phenotype.

Early epidemiological studies estimated the prevalence of CDC at 1 in 50 000 live births, however, recent estimates suggest a greater incidence of 1 in 37 000 live births. It has even been suggested that among the general population with learning disability the prevalence could be as high as 1 in 350. Clearly, given the increasing clinical awareness and hence detection of the syndrome, it is likely that the previously stated rates of administrative prevalence may have been considerably underestimated.

Genetics
CDC results from a deletion of chromatin from the short arm of chromosome 5 (5p). A de novo deletion is present in 85% of cases while 10 to 15% of cases are familial with the overwhelming majority (>90%) due to parental translocations. Although Niebuhr was the first researcher to identify the specific chromosomal region implicated in the syndrome as 5p15.1-5p15.3 using cytogenetic analysis, more recent work has mapped specific critical areas within this region as being responsible for the expression of the core clinical features of the syndrome. For example, the characteristic cat-like cry has been mapped to the proximal part of 5p15.3, the speech delay to the distal part of 5p15.3, and severe intellectual impairment to 5p15.2. The importance of careful characterization of the 5p deletion in a newborn infant suspected of presenting with CDC is further highlighted by the growing number of studies that have described individuals with 5p deletions outside the critical region and who often present with the eponymous cat-cry but not severe learning disability. Such studies highlight the need for accurate differentiation between 5p deletions that result in the typical CDC phenotype and those that result in a milder CDC phenotype and a much more optimistic developmental prognosis.

North American usage: mental retardation.
Physical and medical aspects

Physical features

CDC is also characterized by a range of physical abnormalities and phenotype–genotype studies have demonstrated that these vary according to the size of chromosomal deletion present. Full deletion infants tend to be of low birthweight and show marked hypotonia. Feeding difficulties are common and the associated failure to thrive may be the initial clinical presentation. Some infants may require enteral feeding, a process which may have to continue for several years. Certain facial and head abnormalities are also over represented: microcephaly, micrognathia, rounded face, macrostomia, hypertelorism with downward sloping palpebral fissures, low set ears, broad nasal ridge, and short neck (Figs 1 and 2). These features also appear to correlate in degree with the size of the chromosomal deletion. Structural laryngeal abnormality and hypotonia are thought to be responsible for the cat-like cry (these latter features in addition to high rates of cardiorespiratory abnormalities may present particular problems with anaesthetic procedures). Embryological notochordal origins for the cranial base abnormalities have been postulated. Congenital scoliosis, gastrointestinal and cardiovascular problems (commonly ventricular septal defects, atrial septal defects, and rarely tetralogy of Fallot and endocardial cushion defects) are significantly over represented in affected individuals. The phenotype tends to become less striking with advancing age which may result in diagnostic difficulty in these circumstances; conversely, other features tend to become more apparent such as long face, scoliosis, and macrostomia. Female fertility is unaffected which has important implications for post-pubertal patients. The male to female ratio is 0.73:1. In addition to the major health problems already described, children with CDC are very prone to develop recurrent upper-respiratory tract infections, otitis media, and dental problems. In contrast, the prevalence of epilepsy is very low compared with heterogeneous samples of people with severe learning disabilities. Once individuals manage to negotiate learning disabilities, they can probably expect to live a normal life-span.

Intellectual and cognitive impairments

The early reports on CDC suggested that profound intellectual disability is a cardinal feature of the syndrome, presenting in all individuals with a 5p deletion; however, before 1990 none of the published studies had employed standardized assessment of IQ. It was not known, for example, whether impairment was global or whether there was a performance–verbal discrepancy such as that reported within other genetically disordered syndromes (i.e. fragile X syndrome, Lesch–Nyhan syndrome, and Williams syndrome). Likewise, it was not known whether individuals with atypical CDC (those with deletions outside of the critical region) and who present with a much milder phenotype, display specific cognitive deficits such as developmental language

Figures 1 and 2: Nine-year-old child with typical cri du chat syndrome displaying characteristic physical features but with additional self-injury to face. Parental permission to use photographs obtained.
children with CDC. For example, in a recent study by Cornish and coworkers\textsuperscript{43} over 90% of children with CDC were described by their families as demonstrating troublesome hyperactive behaviour and, of these, 70% fulfilled the diagnostic criteria for attention-deficit–hyperactivity disorder (ADHD). A cross-Atlantic study also revealed a similarly high rate of clinical hyperactivity (over 80%) in a large cohort of 146 children with CDC, and concluded that clinical hyperactivity was one of the most significant and frequent behavioural problems associated with the syndrome.\textsuperscript{31} What is particularly striking about these recent findings is that they contrast so vividly with the commonly portrayed clinical picture of immobility and severe motor delay that was considered to characterize the syndrome since the mid 1960s. The extent to which hyperactivity persists into adulthood in CDC is not known but requires to be investigated further in longitudinal studies.

**Behavioural problems and the effects upon the family**

It has been long recognized that the birth of a child with a severe learning disability can have an impact on all family members including siblings. Indeed, a recent study by Gersh and coworkers\textsuperscript{20} has indicated that many siblings of children with CDC can show a distinct response pattern. This study also reports that the best determinant of familial stress for parents of a child with CDC was the child's level and frequency of behavioural problems. Clearly, further research is needed to assess the effects of modifying influences such as the involvement of family friends or extended social networks (e.g. support groups) in the child rearing in reducing levels of carer stress and thus helping them to cope with their children. Research undertaken in families of children with Smith-Magenis syndrome\textsuperscript{35} and Prader-Willi syndrome\textsuperscript{56} suggests that such external factors can have a moderating effect on the subjective level of parental stress. The UK Cri-du-chat Syndrome Support Group has produced a handbook for parents and professionals with guidelines on available support, advice, and information on problems related to the syndrome.\textsuperscript{29} The UK association also runs special conferences for families which usually include workshops devoted to addressing the issue of coping with the demands of raising a child with CDC.

**Conclusions and future research directions**

It is hoped that this review of the available literature concerning CDC presents a more optimistic picture of the syndrome than that suggested by early researchers. While moderate to severe learning disability remains a core characteristic, the cognitive profile of these children includes a relative strength in receptive language ability. If developed appropriately at a developmentally critical period, enhanced communication skills could contribute to a reduction of the high rates of behavioural problems currently associated with the condition. This would require early recognition and diagnosis of the condition and its variants. This would also result in the early correction of associated health endangering physical abnormalities and would allow early promotion of healthy sleep and other behavioural routines that could further help more children with CDC to optimize their developmental potentials. Detection and early treatment of established behavioural problems (particularly disabling sleep disorders and clinical hyperactivity) using methods already shown to be effective in...
the wider population of children with learning disabilities, should also serve to achieve this principal clinical aim. The need to provide multi-agency support and advice for affected families over several years is also highly important and The UK Cri-du-chat Syndrome Support Group (now in its 10th year) is a major source of help for affected families and their children.

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