

Tuberous sclerosis complex and Wolff-Parkinson-White syndrome

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Abstract

This report highlights the association between tuberous sclerosis and Wolff-Parkinson-White syndrome. Ten patients with concurrent diagnoses of Wolff-Parkinson-White syndrome and tuberous sclerosis were identified. Wolff-Parkinson-White syndrome presented early in life, nine cases being diagnosed in the first year. Eight of the 10 cases were male. In eight cases, the syndrome was associated with supraventricular tachycardias, and in nine with cardiac rhabdomyomata. One child died from cardiac failure secondary to obstruction of the left ventricular out-flow tract by a rhabdomyoma. Five of nine survivors showed resolution of Wolff-Parkinson-White syndrome on follow up. The accessory pathway was localised in nine patients from surface electrocardiograms: six children had left sided pathways and three had right sided pathways.

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Tuberous sclerosis complex is a dominantly inherited genetic disease. The condition shows genetic heterogeneity, with gene loci on chromosomes 9 and 16.^{1,2} Both genes have been identified.^{3,4} Both are tumour suppressor genes, which explains why they apparently produce an identical clinical phenotype characterised by the formation of multiple hamartomas.⁵ Formerly recognised by the clinical triad of epilepsy, mental retardation, and facial angiofibromatosis, it is now appreciated that almost any organ in the body, with the exception of skeletal muscle, may be affected.⁶ The disease is estimated to have a birth incidence of one in 6000 and more than 70% of cases will be new mutations.⁷ Over half the affected individuals will be intellectually normal.⁸ The most common cardiac manifestation of the disease is the cardiac rhabdomyoma, which is thought to occur in at least 60% of children with tuberous sclerosis. The natural history of these tumours is that they regress with increasing age. They may cause no symptoms, but in a minority of cases there may be obstruction of blood flow within the heart.⁹ There have also been a few isolated reports of Wolff-Parkinson-White syndrome occurring in association with tuberous sclerosis (table 1).

Wolff-Parkinson-White syndrome results from the presence of an accessory atrioven-

tricular conducting pathway. It can be diagnosed during sinus rhythm from an electrocardiogram (ECG): there is a shortened PR interval and the QRS complex is deformed and widened in its initial portion by a slow rising slurred deflection called a delta wave. The presence of the accessory pathway predisposes these individuals to an atrioventricular reentry tachycardia. A small proportion of individuals with Wolff-Parkinson-White syndrome will have underlying cardiac disease: ventricular septal defect, Ebstein's malformation of the tricuspid valve, hypertrophic cardiomyopathy, and endocardial cushion defects are the most common associations. It occurs in 0.15% of the general population and in 0.5% of children with cardiac disease.²⁴ However, the intermittent nature of the abnormalities makes it difficult to estimate the prevalence precisely. Patients usually present either in the first year of life or in late childhood or early adult life.

The association of Wolff-Parkinson-White syndrome with tuberous sclerosis is not well known. There have been isolated case reports and references to the association in papers on cardiac rhabdomyomata and tuberous sclerosis (table 1). We now report a series of 10 patients with tuberous sclerosis and Wolff-Parkinson-White syndrome and compare the natural history of this syndrome in tuberous sclerosis and in other situations.

Methods

We sought cases of tuberous sclerosis with a concurrent diagnosis of Wolff-Parkinson-White syndrome, and examined their medical histories to ensure that the diagnosis of tuberous sclerosis met established diagnostic criteria.²⁵ All patients had an ECG record during sinus rhythm that showed a shortened PR interval and a widened QRS complex with a delta wave. We reviewed all available ECGs to confirm the diagnosis and to monitor the natural history of the electrical abnormalities. The anatomical position of the accessory pathways was identified from surface ECGs, using the algorithm described by Fitzpatrick *et al.*²⁶

Results

We identified 10 children with a diagnosis of tuberous sclerosis and Wolff-Parkinson-White syndrome (table 2), five through a prevalence study in the Wessex region, two during a previous national survey of cardiac rhabdomyomata, one through a family genetic linkage study, and two by personal referral. There were eight males and two females. In six of the 10 children Wolff-Parkinson-White syndrome was diag-

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Table 1 Published reports of cases of tuberous sclerosis and Wolff-Parkinson-White syndrome

Author	Ref	Year	Sex	Age at diagnosis	SVT	Cardiac rhabdomyoma
Swiderski	10	1962	M	2 Years	–	–
Martinez	11	1972	M	18 Months	+	–
Milner	12	1980	F	9 Days	–	+
Jayaker	13	1986	M	2 Weeks	+	+
Jayaker	13	1986	M	3 Months	+	–
Casta	14	1986	F	Birth	+	+
Schneider	15	1986	M	9 Months	+	+
Yamashita	16	1987	M	4 Days	+	+
Chitiyat	17	1988	M	Birth	–	+
Manetti	18	1989	M	7 Years	?	+
Manetti	18	1989	F	3 Years	?	+
Harding	19	1990	M	5 Months	+	+
Mehta	20	1993	F	36 Hours	+	+
Mehta	20	1993	F	2 Days	+	+
Abushaban	21	1993	?	?	+	–
Ijaola	22	1994	F	24 Years	–	–
Nir	23	1995	?	6 Months	–	+
Nir	23	1995	?	6 Months	–	+

SVT = supraventricular tachycardia; ? = information not provided in paper.

Table 2 Study cases of Wolff-Parkinson-White (WPW) syndrome and tuberous sclerosis

Case No	Sex	Age at diagnosis	SVT	Cardiac rhabdomyoma	Follow up/ ECG	Age at follow up
1	M	1 Day	+	+	Normal	8 Years
2	M	9 Days	–	+	N/A	Died
3	M	2 Months	+	+	WPW	7 Years
4	F	1 Day	+	+	Normal	14 Years
5	M	10 Months	+	+	WPW	6 Years
6	M	1 Day	–	+	Normal	4 Years
7	M	1 Day	+	+	Normal	3 Years
8	M	1 Day	+	+	Normal	2 Years
9	M	1 Day	+	+	WPW	1 Month
10	F	3.5 Years	+	–	WPW	3 Years, 10 months

SVT = supraventricular tachycardia.

Table 3 Localisation of accessory pathways from surface ECG

Case No	Site of accessory pathway
1	Left lateral
3	Right posteroseptal
4	Right anteroseptal
5	Left posterolateral
6	Left posteroseptal
7	Left posteroseptal
8	Extreme left lateral
9	Left posterolateral
10	Right posterolateral

In case No 2 the pathway was not localised, as a full 12-lead ECG was not available.

nosed on day 1, and in all but one the diagnosis was made within the first year of life. A supraventricular tachycardia was the presenting feature in four of the six who were diagnosed on day 1. Eight of the children eventually developed supraventricular tachycardias. All the children were investigated with echocardiograms and nine had evidence of cardiac rhabdomyomata.

Length of follow up ranged from one month to 14 years (median follow up time was four years). One child died aged 30 days from cardiac failure secondary to ventricular outflow obstruction by a cardiac rhabdomyoma. Two children underwent successful cardiac surgery for removal of rhabdomyomata, one for obstruction of the tricuspid valve and the other for obstruction of the left ventricular outflow tract. Follow up ECGs were obtained from the nine survivors and showed resolution of the Wolff-Parkinson-White syndrome in five. The accessory pathway was localised in nine children (table 3): six had a pathway on the left side of the heart and three on the right. We were unable to localise the pathway in patient No 2 because a full 12-lead ECG was not available.

Discussion

This is the largest collection of tuberous sclerosis patients with Wolff-Parkinson-White syndrome published to date. The prevalence of this syndrome in tuberous sclerosis is unknown and cannot be determined from our study. A recent review of tuberous sclerosis and cardiac

rhabdomyomata suggested that 9–13% of patients with rhabdomyomata have the Wolff-Parkinson-White syndrome, but this was in a selected hospital based population.²³ In a study conducted in the south of England in 1996, 131 cases of tuberous sclerosis were identified, among whom there were two with symptomatic Wolff-Parkinson-White syndrome who were alive on the census date⁸; this suggests a possible prevalence of 1.5% in tuberous sclerosis, compared with 0.15% (both symptomatic and asymptomatic) in the general population.²⁴

We found evidence of sex bias in cases of Wolff-Parkinson-White syndrome and tuberous sclerosis (eight males, two females), and there seems to be a similar male bias in cases of rhabdomyomata and tuberous sclerosis—in Nir's study of cardiac rhabdomyomata and tuberous sclerosis from the Mayo clinic, 60% of cases were male.²³ Wolff-Parkinson-White syndrome in the general population also appears to be more common in males than in females: Sherf and Neufeld reviewed 23 series from the literature and found that 65% of the cases occurred in males.²⁷

The aetiology of Wolff-Parkinson-White syndrome in tuberous sclerosis has not been explained. It has been known for some time that some of the cells in the cardiac rhabdomyomata found in patients with tuberous sclerosis are structurally identical to normal Purkinje cells, so it has been presumed that rhabdomyomatous tissue traversing the atrio-ventricular junction acts as the accessory pathway bypassing the atrioventricular node.²⁸ This theory is compatible with the results of our survey. All but one of our patients had echocardiographic evidence of cardiac rhabdomyomata. There are four published cases of Wolff-Parkinson-White syndrome occurring in tuberous sclerosis apparently without cardiac rhabdomyomata, but two of these cases were reported before echocardiography became a routine investigation, so a rhabdomyoma could have been missed.^{10,11} In a third case, aged 3 months at diagnosis, and in case number 10 in our series, who was 3.5 years old at diagnosis, it is possible that rhabdomyomatous tissue could already have regressed by the time of echocardiography, as we have seen large rhabdomyomata completely disappear on echocardiogram within a period of six weeks from birth.¹³ It is also likely that some cardiac rhabdomyomata may be too small to be seen on echocardiography.

Our cases show a high resolution rate on at least one follow up ECG (five of nine survivors), compared with Wolff-Parkinson-White syndrome in the general population. Resolution of Wolff-Parkinson-White syndrome over time is well documented: in a longitudinal study of 42 children by Swiderski *et al*, six resolved.¹⁰ Gillette *et al* report that 29% of their sample of 98 patients with Wolff-Parkinson-White syndrome had no evidence of pre-excitation on multiple follow up ECGs,²⁴ while Perry *et al* found that 26% of their series of 140 patients lost their pre-excitation pattern.²⁹ The higher rate of resolution of Wolff-Parkinson-White syndrome in tuberous

sclerosis patients could be explained by the fact that rhabdomyomata are known to regress over time and therefore the accessory pathway may disappear or cease to conduct. However, there is at least one reported case of Wolff-Parkinson-White syndrome in an adult with tuberous sclerosis.²²

Our study highlights the association between tuberous sclerosis and supraventricular tachycardia, with overt pre-excitation visible on the ECG. Tuberous sclerosis may also be associated with supraventricular tachycardias in the absence of overt pre-excitation, though probably less often. In researching this paper we discovered one additional tuberous sclerosis patient with a supraventricular tachycardia and a short PR interval on ECG but no evidence of a delta wave. This patient presented on day 1 of life and did have cardiac rhabdomyomata. It is likely that the underlying mechanism for his arrhythmia was the same as in the patients with tuberous sclerosis and Wolff-Parkinson-White syndrome, but that his accessory pathway was concealed.

The hypothesis that Wolff-Parkinson-White syndrome in tuberous sclerosis may be caused by something which is present early in life but which later resolves is supported by the fact that all but one of our cases presented within the first year of life and six of 10 presented on day 1. Eight of 10 patients developed symptomatic arrhythmias, all supraventricular tachycardias. Symptomatic cases responded well to conventional drug treatment chosen by their local physician. Wolff-Parkinson-White syndrome in this group of tuberous sclerosis patients was not life threatening and resolved over time in the majority. However, serious complications are possible, both in utero and in infancy.

The association of cardiac rhabdomyomata and fetal hydrops has been described.³⁰ There are two possible mechanisms. First, rhabdomyomata may cause severe obstruction within the heart, leading to cardiac failure. Second, rhabdomyomata may provoke fetal arrhythmias which in turn lead to cardiac failure. Several different types of arrhythmia have been described in the fetus in combination with cardiac rhabdomyomata (with or without tuberous sclerosis), and two of these cases had fetal supraventricular tachycardias.^{31 32} Neither was proven to have tuberous sclerosis but there is no reason to doubt that a fetus with tuberous sclerosis could develop an atrioventricular reentry tachycardia related to Wolff-Parkinson-White syndrome, leading to heart failure and hydrops.

Sudden unexpected death in infancy has been documented in tuberous sclerosis. This has been attributed to a cardiac cause, following exclusion of neurological causes and because multiple rhabdomyomata were found at necropsy, but no precise cardiac mechanism has been elucidated.²³ It is possible that some of these fatalities may be caused by atrial arrhythmias which, when associated with anterograde conduction down an accessory pathway, provoke ventricular fibrillation. A child with tuberous sclerosis and cardiac rhabdomyomata

has been reported with clinical progression from supraventricular tachycardia to ventricular fibrillation to death, which could be explained by this mechanism.¹⁶ Case *et al* have reported on a 9 month old child with multiple rhabdomyomata presenting with complex supraventricular and ventricular arrhythmias who was resistant to medical treatment and subsequently died of congestive heart failure.³³ These complications are clearly rare.

In conclusion, we have highlighted the association between Wolff-Parkinson-White syndrome and tuberous sclerosis. This occurs more often in males and almost exclusively in association with cardiac rhabdomyomata. It presents early in life, often on day 1, and is usually associated with symptomatic supraventricular tachycardia. It responds well to medical treatment and a high proportion of cases will resolve over time. In this series the complication did not cause serious morbidity, but in rare instances serious complications could occur. Infants diagnosed with tuberous sclerosis should always have an ECG to exclude the possibility of pre-excitation.

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